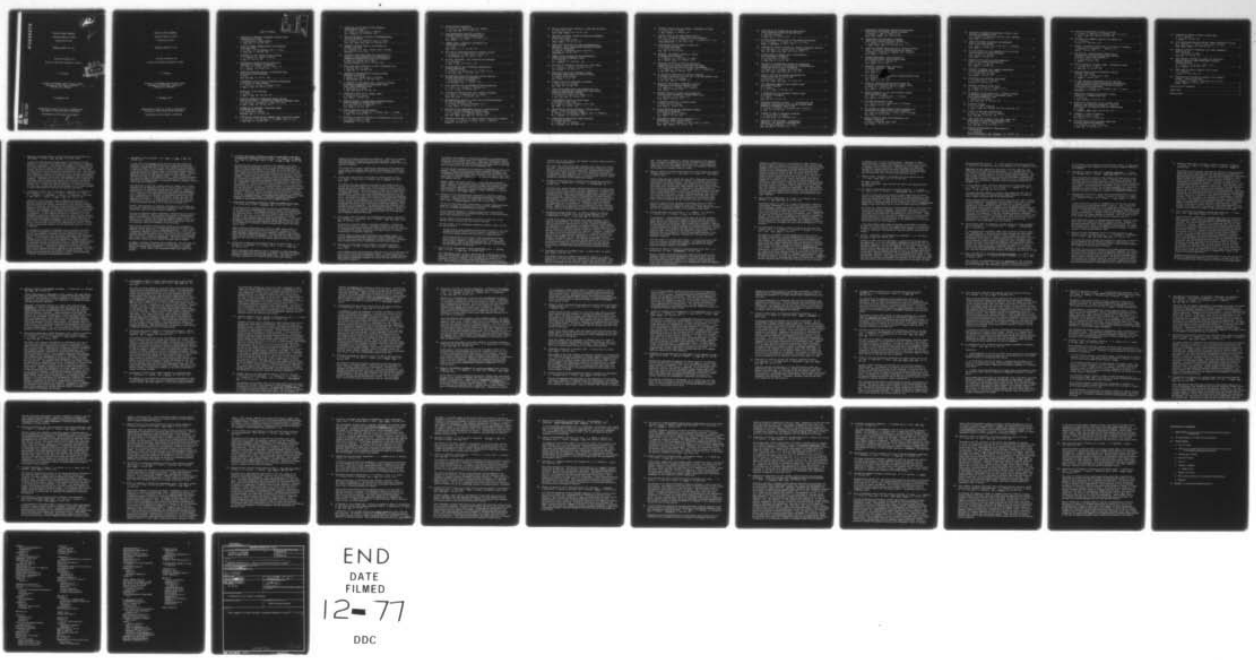
AD-A046 278 OKLAHOMA UNIV HEALTH SCIENCES CENTER OHLAHOMA CITY D--ETC F/G 6/16
ABSTRACT REFERENCE LIST: REVIEWS OF PERTINENT LITERATURE IN SHO--ETC(U)
SEP 77 L B HINSHAW N00014-76-C-0229
UNCLASSIFIED TR-120 NL

1 OF 1
AD A046278



END
DATE FILMED
12-77
DDC

12

OFFICE OF NAVAL RESEARCH

Contract N00014-76-C-0229

Project NR 207-040

TECHNICAL REPORT NO. 120

Abstract Reference List

Reviews of Pertinent Literature in Shock

L. B. Hinshaw

University of Oklahoma Health Sciences Center
Department of Physiology & Biophysics
Oklahoma City, Oklahoma

27 September 1977

(see 1473)

OFFICE OF NAVAL RESEARCH

Contract N00014-76-C-0229

Project NR 207-040

TECHNICAL REPORT NO. 120

Abstract Reference List

Reviews of Pertinent Literature in Shock

L. B. Hinshaw

University of Oklahoma Health Sciences Center
Department of Physiology & Biophysics
Oklahoma City, Oklahoma

27 September 1977

TABLE OF CONTENTS

1. Depression of pancreatic bicarbonate response during endotoxic shock in dogs. L. Greenberg and S. Shimo-Takahara. J. Surg. Res. 21: 425-428, 1976.

Upper gastrointestinal erosions have been a significant clinical finding subsequent to septic or endotoxic shock. Gastric acid as an integral factor in the stress ulcer syndrome is crucial to the formation of acute gastric erosions both in man and in the dog. Recent experiments have demonstrated that endotoxin-induced shock severely reduces the ability of the canine proximal duodenum to clear or neutralize hydrochloric acid (HCl). The two main mechanisms by which HCl is cleared from the duodenum are neutralization by pancreatic bicarbonate (HCO_3), and transmural absorption of the hydrogen ion. Greenberg and Himal noted a significant decrease in both the amount of hydrogen ion lost transmurally and in the amount neutralized and diluted by mixed bile and pancreatic juice secretions in canine duodenal pouches during endotoxic shock. This decreased clearance was associated with the formation of acute duodenal erosions. Experiments were done with the intent of quantitating the role of the pancreas in the neutralization of HCl during endotoxic shock in dogs.

Within 2 hr of endotoxin administration, both primary mechanisms of duodenal H^+ clearance are severely depressed. The defects described in this and in previous reports from this laboratory are similar to factors described in the literature as related to the pathogenesis of chronic duodenal ulcer in humans. These are: limited ability of the duodenal mucosa to synthesize and/or release secretion, less HCO_3 production for a given amount of acid input, or an increased pancreatic threshold to secretin.

2. Effect of induced thrombocytopenia on experimental circulatory shock. A. M. Lefer, G. A. Bridenbaugh, and J. T. Flynn. J. Surg. Res. 21: 429-436, 1976.

Platelets have received renewed attention in a variety of acute disease states, largely due to the acquisition of information concerning release reactions and the aggregation phenomena. Alterations in these platelet responses may be important in the development of intravascular thrombosis. In this regard, platelet aggregation in the microcirculation has been found to be a significant occurrence in organ damage during ischemic states including shock.

Thrombocytopenia (i.e., a circulating platelet count of 20% of normal) was induced in dogs by glass contact perfusion. Splanchnic artery occlusion (SAO) shock was then induced in thrombocytopenic as well as in sham-thrombocytopenic dogs. Thrombocytopenia significantly attenuated the early postrelease increase in SFP, an observation indicative of a reduced formation of platelet aggregates in response to the shock state. However, thrombocytopenia did not significantly alter the heart rate, superior mesenteric artery flow, or portal venous pressure response to SAO shock. Mean arterial blood pressure was transiently higher in the thrombocytopenic dogs (i.e., 5 min after release) but this difference soon disappeared. Plasma accumulation of prostaglandin E and F_{2a}; the lysosomal protease; cathepsin D; and the toxic factor, MDF, were not modified by thrombocytopenia in shock dogs. These data suggest that neither platelet release of

humoral substances nor platelet aggregation are primary mechanisms in the development of the shock state. The data also indicate that removal of a large number of circulating platelets does not confer protection during SAO shock. These findings, however, do not rule out a secondary role of platelets in the pathophysiology of SAO shock.

3. Complement and host defense against infection. R. B. Johnston, Jr., and R. M. Stroud. J. Ped. 90: 169-179, 1977.

Knowledge of the biochemistry and physiology of the complement system has grown dramatically in recent years. Understanding of the function of complement and application of this understanding to the care of patients have been greatly improved by the careful evaluation of human beings and animals with disorders of this system. In its essence, this new knowledge clearly indicates that the complement system is one of the principal mediators of the inflammatory response and, thereby, serves an essential function in host defense against infection. After a brief review of the biochemistry and physiology of complement as background, we will attempt to summarize current knowledge that relates to the activity of this system in resistance in infection.

Because of the essential nature of the complement system in host defense against infection, a defect of complement function should be considered in any patient with an unusual pattern or frequency of infections or with collagen-vascular disease. The frequency with which complement disorders are being detected in such patients by an abnormality of the relatively simple hemolytic complement assay argues strongly that this procedure should be available as a screening test to every physician. As more defects are detected and carefully characterized, important information should be gained regarding the functions of the complement system in the maintenance of health and the mediation of disease.

4. Physiological inhibition and facilitation of adrenocortical response to hemorrhage. D. S. Gann, G. L. Cryer, and J. C. Pirkle, Jr. Am. J. Physiol. 232: R5-R9, 1977.

In a search for physiological feedback inhibition, secretion rates of cortisol were measured in intact dogs before and after sequential hemorrhages. The second of two sequential hemorrhages of 10 ml/kg separated by 90 min evoked significantly less increase of secretion rate of cortisol than did the first. This result was not explained by differential hemodynamic effects. Exhaustion of pituitary of adrenal capacities was excluded, since dogs responded normally to a second, larger hemorrhage. However, no attenuation of response to a second 10 ml/kg hemorrhage was seen after a larger, 20 ml/kg, first hemorrhage. This led in turn to a search for a physiological facilitatory mechanism which might offset the feedback effect. The second of two rapid sequential hemorrhages to isovolemia following preexpansion of plasma volume evoked significantly greater increase of secretion rate of cortisol than did the first. This result also was not explained by differential hemodynamic effects. The results support the hypothesis that hemorrhage elicits both physiological feedback and facilitatory effects which interact and which are (different) functions of the intensity of stimulus.

5. Leucocytes containing bacteria in plain blood films from patients with septicaemia. H. Smith. Aust. Ann. Med. 15: 210-221, 1966.

   A search for infected cells was made with the low power (X10 or X20) objective in plain blood films from patients known to have, or suspected of having, septicaemia. It was found that scanning of a film in this way for a short time will detect even small concentrations of infected cells. Infected leucocytes occurred in highest concentration in the first drop of blood issuing from the previously unmanipulated ear lobe. They occurred most frequently in films in which there was also an increase in mononuclear cells containing inclusions of corpuscular origin, and were found whether or not the patient had recently been given apparently effective antibiotic treatment. Consideration is given to the requirements for a diagnosis of septicaemia from the presence of infected cells in blood films and the distinction of bacteria from other structures in leucocytes which may resemble them. A search for infected leucocytes in a plain blood film of the first drop of blood from the ear lobe appears to be a useful procedure in routine investigation of patients who may have septicaemia.

6. A randomized clinical trial of granulocyte transfusions for infection in acute leukemia. J. B. Alavi, R. K. Root, I. Djerassi, A. E. Evans, S. J. Gluckman, R. R. MacGregor, D. Guerry, A. D. Schreiber, J. M. Shaw, P. Koch, and R. A. Cooper. N. Engl. J. Med. 296: 706-711, 1977.

   Infection is one of the major causes of morbidity and mortality in patients with granulocytopenia. The introduction of newer antibiotic drugs has improved the outlook substantially in such patients, although most of the drugs are less effective in the presence of granulocytopenia. Therefore, the transfusion of normal granulocytes appears to be a rational addition to the management of infection in neutropenic hosts. Excellent, controlled data in animal models indicate that granulocyte transfusions are beneficial: in dogs rendered neutropenic by irradiation or cyclophosphamide, granulocyte transfusions have been shown to prevent naturally acquired septicemia, and to prolong survival and produce some cures after the induction of pseudomonas pneumonia. It has been more difficult to show a clear-cut benefit of neutrophil transfusions in the more complex clinical settings seen in patients with granulocytopenia due to a variety of drugs or bone-marrow diseases and with infections caused by a variety of organisms.

   In a prospective, controlled, randomized study to evaluate the efficacy of filtration-leukapheresis granulocytes in granulocytopenic febrile patients with leukemia, 19 patients received antibiotics alone, and 12 received antibiotics plus daily granulocyte transfusions from ABO-matched donors. In skin-chamber studies the granulocytes appeared at sites of inflammation for at least 6 hr after transfusions. Infected subjects survived longer if they received granulocytes. Differences between control and transfused patients were greatest in patients with persistent bone-marrow failure, the 21-day survival being 20% in controls, and 75% in transfused patients. Granulocytes appeared to have no effect on the outcome of febrile episodes in which infection was not documented, the 21-day survival being 79% for controls and 88% for transfused patients. The transfusion of granulocytes thus appears to offer a survival advantage to infected, persistently granulocytopenic patients.

7. Neutrophils in the blood bank. D. R. Boggs. N. Engl. J. Med. 296: 748-750, 1977.

In this issue of the Journal, Herzig and Alavi and their respective associates (see abstracts #6 and #8 in this volume) provide the most definitive evidence published to date that transfusion of neutrophils is a beneficial adjunct in the treatment of infected, neutropenic patients. As the authors state, previous studies have provided convincing data in laboratory animals and suggestive data in man on this benefit. However, I agree with the authors that previous reports of human studies have suffered from flaws in experimental design. I doubt if anyone knowledgeable about neutrophils and their role in combating infections has ever doubted that an adequate number of acequately function, adequately matched cells would prove beneficial.

One should bear in mind that a normal person has roughly half of blood neutrophils in the marginal pool--that is, they are stuck to or rolling along the walls of capillaries and postcapillary venules. Leukocyte determinations on venous blood samples do not include these marginated cells. There may be a normal physiologic mechanism by which the proportion of marginated cells increases as neutropenia becomes more severe. Thus, transfused cells in severely neutropenic patients may enter the marginal pool primarily. A second possibility is that the first time transfused cells pass by the infected area, they are simply induced to be here sequestered and thus be in circulation for minutes only.

Current, crude technology in neutrophil transfusion, if used under the best current conditions, can increase the probability that a neutropenic patient will survive a serious bacterial infection.

This type of controlled study of neutrophil transfusion has not received universal acclamation. Herzig indicates this point in an unreferenced phrase, "Arguments have been made that a randomized control study is unnecessary..." However, this rather gentlemanly treatment of the criticisms that have been directed toward this type of controlled study does not accurately reflect the vehemence of the criticisms.

Herzig and his associates studied proved infection with gram-negative organisms whereas Alavi et al. included some patients with fever in whom infection was not proved (fever of undetermined origin). In the later circumstance transfusion was of no evident benefit. One of the most time-consuming and difficult studies that I have ever done was a double-blind trial of antibiotic therapy in patients with cancer and fever of undetermined origin, most of whom were neutropenic. The results indicated that antimicrobial therapy was of no benefit and might even be harmful.

In summary, neutrophil transfusion can be beneficial, but at present the magnitude of the problems that attend it dictates that it will prove useless and perhaps even detrimental if it is considered a "routine" procedure. I hope, however, that continued research will negate this opinion.

8. Successful granulocyte transfusion therapy for gram-negative septicemia. A prospectively randomized controlled study. R. H. Herzig, G. P. Herzig, R. G. Graw, Jr., M. I. Bull, and K. K. Ray. N. Engl. J. Med. 296:701-705, 1977.

The mortality from infection in patients with compromised bone-marrow function remains high despite the use of broad-spectrum antibiotics. In 1931, the clinical implications of neutropenia as an etiologic factor in rapidly fatal bacterial infections were noted, but it was 35 years later that a quantitative relation was demonstrated between the level of circulating granulocytes and the prevalence of infection for patients with acute leukemia. Twenty-seven granulocytopenic patients who experienced a total of 30 episodes of gram-negative septicemia were prospectively randomized. The control group received an appropriate antibiotic regimen alone, whereas the "transfusion" group received infusions of granulocytes in addition to the antibiotics. Five of 14 controls survived, and 12 of 16 in the transfusion group survived ($p<0.04$). An important factor in the outcome of treatment was the recovery of bone-marrow function (return of peripheral granulocyte count>1000/μl). Eighty-three % of the control group and all of the transfusion group with recovery of granulocyte levels survived the episode of sepsis. In contrast, none of the eight control patients, as compared to 67% of the transfusion group, survived persistent granulocytopenia ($p< 0.005$). Granulocyte transfusions appear to complement appropriate antibiotic treatment of gram-negative-septicemia due to granulocytopenia.

9. Interactions of neutrophil granulocytes (PMNs) and endothelium in vitro. J. M. Lackie and D. De Bono. Microvasc. Res. 13: 107-112, 1977.

One of the earliest observable events in the acute inflammatory reaction is the adhesion of polymorphonuclear leucocytes (PMNs) to the endothelium of capillary vessels. This margination process has been described in vivo, but relatively little is known about the adhesive interaction which is presumed to take place, nor is much known of the cellular activities involved in the subsequent phase of emigration (diapedesis). In this paper in vitro observations are presented which suggest that endothelial cells may provide a particularly good substrate for PMN adhesion and that there is no inhibition of locomotion of PMNs following their contact with endothelial cells.

Rabbit peritoneal polymorphonuclear leucocytes (PMNs) adhere readily to serum-coated glass and to the surfaces of pig aortic endothelial cells grown in vitro, though adhesion to pig fibroblast surfaces is much weaker. Using time-lapse cinephotomicrography it has been shown that PMNs will move freely over the surfaces of endothelial cells and that they show no contact paralysis when they collide with the leading lamella of moving endothelial cells.

10. Intravascular coagulation and pulmonary edema in the septic baboon. J. W. Holcroft, F. W. Blaisdell, D. D. Trunkey, and R. C. Lim. J. Surg. Res. 22: 209-220, 1977.

Labeled autologous fibrinogen was used in 18 baboons to study fibrinogen kinetics and deposition of fibrin and its products in the organs of animals subjected to deep septic and deep hemorrhagic shock. The half-life of fibrinogen shortened to 5% of control values in the septic animals,

compatible with marked intravascular coagulation. Fibrin and its products were deposited in the lungs and in the liver and spleen. The lungs developed pulmonary edema and demonstrated an increased tendency for extravasation of albumin.

This association of sepsis, intravascular coagulation, fibrin deposition in the lungs, and pulmonary edema supports the hypothesis that the lung damage in sepsis is mediated, at least in part, by intravascular coagulation.

11. Glucose and lactate kinetics after endotoxin administration in dogs. R. R. Wolfe, D. Elahi, and J. J. Spitzer. Am. J. Physiol. 232: E180-E185, 1977.

The effects of E. coli endotoxin on the glucose and lactate kinetics in dogs were studied by means of the primed constant infusion of [6-^{3}H] glucose and Na-L-(+)-[U-^{14}C]lactate. The infusion of endotoxin induced a transient hyperglycemic level, followed by a steady fall in plasma glucose to hypoglycemic levels. The rate of appearance (R_a) and the rate of disappearance (R_d) of glucose were both significantly elevated ($p<.05$) for 150 min after endotoxin, after which neither differed from the preinfusion value. The metabolic clearance rate of glucose was significantly elevated at all times 30 min postendotoxin. By 30 min postendotoxin, R_a and R_d of lactate, plasma lactate concentration, and the percent of glucose turnover originating from lactate were significantly elevated and remained so for the duration of the experiment. We concluded that after endotoxin hypoglycemia developed because of an enhanced peripheral uptake of glucose and a failure of the liver to maintain an increased R_a of glucose. We also concluded that lactate became an important precursor for gluconeogenesis and an important metabolic substrate.

12. The in vitro effect of steroids on polymorphonuclear leukocyte metabolism. M. R. Cooper, L. R. DeChatelet, and C. E. McCall. Proc. Soc. Exptl. Biol. Med. 141: 986-990, 1972.

Steroids have a profound effect on neutrophil metabolism. Although the basic site of action is uncertain, the defects observed might well lead to decreased intracellular bactericidal activity which in turn could explain why corticosteroid therapy in patients occasionally leads to increased susceptibility to bacterial infections.

Steroids added in vitro to human neutrophils have numerous effects on cellular metabolism, including inhibition of hexose monophosphate shunt activity, particle uptake, and iodination of zymosan particles. The magnitude of these effects varies considerably with the steroid employed.

13. Neutrophil and band counts in the diagnosis of neonatal infections. G. I. Akenzua, Y. T. Hui, R. Milner, and A. Zipursky. Pediatrics 54: 38-42, 1974.

In the newborn period severe bacterial infections still carry a high mortality rate in spite of available antimicrobial agents. As early indication of infections in neonates may be indefinite with nonspecific symptoms and signs, early diagnosis and prompt treatment are crucial for survival and for the prevention of sequelae.

An increase in the number of circulating neutrophils with predominance of young forms (the so-called shift to the left) is a characteristic feature of patients with bacterial infections. Accordingly, the present study was carried out to assess the value of neutrophils and band counts in the diagnosis of infection in the first days of postnatal life.

A system has been developed for the evaluation of hematological data in the newborn. Normal values were established for segmented (neutrophil) and nonsegmented (band) polymorphonuclear leukocytes in the peripheral blood of 169 healthy full-term infants during the first five days of life. This normal data is displayed graphically and the values for infants under study are compared directly.

Newborn infants with proven bacterial infections had normal neutrophil counts; however, the band counts increased significantly beyond the normal range. Therefore, the simple laboratory procedure for ennumerating band neutrophils with comparison of absolute values and changes to a normal range represents a hematologic technique of major importance in the diagnosis of sepsis of the newborn infant.

14. Influence of sera from guinea pigs intoxicated by a bacterial lipopolysaccharide on the respiration and carbohydrate metabolism of guinea pigs leucocytes. (English title of of French paper by M. Henon, A. Delaunay, and S. Bazin in Biologic Medicale (Paris) 57: 471-519, 1968.)

(1) The sera from guinea pigs, intoxicated by a typhoid lipopolysaccharide, stimulate, in vitro, the respiration and even more the carbohydrate metabolism of normal polymorphonuclear leucocytes.

(2) The observed stimulation is already obvious with a serum obtained 4 hours after the injection of lipopolysaccharide and is still more obvious with a serum obtained 48 hr later.

(3) The increase of the respiration is only due, in each case, to the abnormal levels of glucose and lactic acid in the sera.

(4) The increase of the carbohydrate metabolism, however, seems to be due to several factors:

(a) One of them, whose influence would be almost exclusive in the serum obtained four hours after the toxic injection, is ascribed to a desequilibrium between glucose and lactic acid, as mentioned above.

(b) The same factor is still active in the serum obtained 48 hours after the toxic injection. However, others are also active. These would be able to enhance the hexokinase activity. As it appeared in our experiments, they increase the anaerobic glycolysis and the intracellular glycogenesis in leucocytes.

15. Renal blood flow distribution in septic hyperdynamic pigs. T. Ravikant and C. E. Lucas. J. Surg. Res. 22: 294-298, 1977.

Acute hyperdynamic sepsis in man is associated with increased renal blood flow (RBF) and polyuria, presumably due to high RBF to the medulla causing washout of interstitial osmoles. This presumption was studied in 14 hyperdynamic piglets with hindlimb sepsis and compared to 11 control piglets. RBF distribution was measured by ^{51}Cr-labeled microspheres previously

injected into the left ventricle and compared to cardiac output measured by rate of isotope disappearance.

Both septic and control piglets had comparable vital signs at the time of the study. Cardiac output and RBF were significantly increased in septic piglets; cortical flow was also significantly increased whereas medullary flow was only slightly increased. These data demonstrate that polyuria in hyperdynamic septic piglets is not due to interstitial medullary washout secondary to increased medullary flow. Polyruia probably reflects tubular dysfunction unrelated to renal hemodynamic changes.

16. Influence of phenylbutazone on leukocyte glucose metabolism and function. B. Kjøsen, H. H. Bassøe, and C. O. Solberg. J. Reticuloendo. Soc. 20: 447-455, 1976.

In recent years, several disease syndromes characterized by chronic infections have been related to defects in either phagocytosis or intracellular killing of bacteria and fungi by neutrophil granulocytes. Evidence is now accumulating that commonly used therapeutic agents might influence granulocyte function also. The influence of phenylbutazone on human leukocyte glucose metabolism, phagocytosis and intracellular killing of bacteria has been examined. A marked inhibition of CO_2 production and intracellular killing of bacteria was observed. The reduction in lactate production and phagocytosis was less pronounced. In phagocytizing cells, phenylbutazone significantly reduced the glucose entering the pentose phosphate pathway. Whether these impairments of leukocyte function also take place in vivo resulting in enhanced susceptibility to infection remains unknown.

17. An improved in vitro pyrogen test: To detect picograms of endotoxin contamination in intravenous fluids using Limulus amoebocyte lysate. R. Nandan and D. R. Brown. J. Lab. Clin. Med. 89: 910-918, 1977.

A method for in vitro pyrogen testing using Limulus amoebocyte lysate (LAL) has been described. The method is based upon the measurement of endotoxin-precipitable protein and can be used to measure picogram quantities equivalent to E. coli endotoxin in unknown solutions. When increasing concentrations of E. coli endotoxin are added to a constant amount of LAL and the reaction is allowed to proceed to completion, there is a proportional increase in the protein precipitated by endotoxin. Therefore, by measuring the amount of protein precipitated from LAL, it is possible to determine the equivalent E. coli endotoxin concentration in unknown solutions, when samples of the unknowns are run simultaneously with E. coli endotoxin standards and negative controls. The endotoxin proportional precipitation of protein occurs in reaction mixture showing gelation as well as in reaction mixture where the levels of endotoxin are lower than required for gelation. Determination of precipitated protein provides greater sensitivity for endotoxin detection than the gelation methods currently in use.

18. Indomethacin protection in traumatic shock. S. Halevy and B. M. Altura. Circ. Shock 3: 299-302, 1976.

Pretreatment of mice with different dose-duration regimens of a prostaglandin (PG) synthetase inhibitor, indomethacin, exerted significant early protection (i.e., up to 2 hr) after Noble-Collip drum trauma (NCDT). Indomethacin pretreatment did not, however, improve long term survival after

NCDT. These results suggest that synthesis and release of PG compounds early in trauma may contribute to the high incidence of early mortality seen after NCDT. Our data support the notions that: 1) PG molecules may indeed play a role in circulatory shock; and 2) PG synthetase inhibitors may be useful as an adjunct therapy in trauma.

19. Metabolic effects of glucose-insulin-potassium infusion during experimental intraperitoneal sepsis. N. T. Ryan and G. H. A. Clowes, Jr. Circ. Shock 3: 309-313, 1976.

Control fasted and septic fasted rats were given either saline or glucose-insulin-potassium (GIK) infusions to evaluate the metabolic response of heart, muscle, and adipose tissues. GIK resulted in an elevation of heart and adipose tissue pyruvate dehydrogenase (PDH) activity in both control fasted and septic fasted animals, when compared with saline-infused controls. This response was accompanied by a reduction in circulating fatty acid levels in GIK-infused groups. In contrast, diaphragm PDH failed to increase after GIK administration to the septic animals, but did increase after GIK in the control fasted group. In the saline-infused groups, heart and adipose tissue PDH activities were higher (almost 2-fold) and fatty acids lower (almost one-half) in the septic fasted than in the control fasted animals, whereas diaphragm PDH was essentially the same in both groups.

These data suggest insulin resistance in diaphragm, but not in heart or adipose tissue during intra-abdominal sepsis, and provide new, direct evidence for a metabolic response to GIK by heart. These changes may contribute to the cardiovascular effects of GIK infusion during sepsis.

20. Serratia marcescens and the urologist. S. D. Madduri, D. A. Mauriello, L. G. Smith, and J. J. Seebode. J. Urol. 116: 613-615, 1976.

S. marcescens is a normal commensal of the bowel and the skin of humans. Until recently S. marcescens was regarded as being relatively harmless to humans and was even inoculated in humans to demonstrate bacteremia after dental extractions and bacteriuria after urinary tract procedures. However, its pathogenicity has now become a matter of increasing concern and Serratia is being isolated from clinical specimens with increasing frequency. Serious infections have been recorded in the respiratory tract, in burn patients, surgical wounds, arterial grafts and patients with endocarditis. S. marcescens has been recorded as a cause of gram-negative endotoxic shock, meningitis after lumbar puncture, osteomyelitis, septicemia and fatal transfusion reaction.

From this study it is evident that Serratia is a serious nosocomial infection in the elderly and debilitated patient. All symptomatic patients should be vigorously treated with appropriate antibiotics and proper preventive measures should be instituted.

21. Protection of hypoxic cytotoxicity by glucocorticoid in the liver. R. P. Carlson and A. M. Lefer. Inflammation 1: 347-357, 1976.

Hypoxia, ischemia, and acidosis are local conditions which occur in the splanchnic region during the development of circulatory shock. We have previously found in isolated perfused cat livers that hypoxia alone produced the most deleterious effects (e.g., depresses reticuloendothelial system (RES) clearance and elevated lactic dehydrogenase (LDH) and cathepsin D activities in the perfusate).

Induction of hypoxia for 2.5 hr in perfused cat livers resulted in a 10-fold increase in cathepsin D and a 15-fold increase in lactic dehydrogenase (LDH) activities in the perfusate and a 42% depression of the clearance rate of particles by the reticuloendothelial system (RES). Addition of 10^{-3} M methylprednisolone (MP) to the perfusate only slightly retarded the release of LDH, but significantly ($p<0.05$) inhibited cathepsin D release by 90% at 150 min. Liver flow did not change during the perfusion period when MP was added to control or hypoxic livers. Similarly, MP did not significantly alter oxygen consumption in perfused livers. However, MP protected against the reduction in carbon clearance during hypoxia without inducing blockade of colloidal carbon clearance. Moreover, opsonization of carbon with autologous plasma did not improve the clearance of colloidal carbon above that observed in nonopsonized experiments. Thus, pharmacologic doses of a synthetic glucocorticoid protected RES cells and release of lysosomal hydrolases during severe hypoxia in isolated perfused cat livers probably by stabilization of cellular and intracellular (lysosomal) membranes.

22. Heparin-induced coagulopathy. W. R. Bell, N. D. Anderson, and A. O. Anderson. J. Lab. Clin. Med. 89: 741-750, 1977.

Intravenous heparin, at doses of 3.0 U/gm of body weight, produced an intravascular coagulopathy in rats which was manifested by intestinal tract hemorrhage, a reduction in plasma fibrinogen concentration, a rise in fibrinogen-fibrin degradation products, and the absence of a rise in platelet count noted in the control animals. This coagulopathy could not be produced by conventional anticoagulant doses of heparin or the injection of large doses of heparin in the presence of protamine sulfate. Specific studies excluded hypoxemia, metabolic acidosis, and endotoxemia as possible etiologic factors. The coagulation abnormalities observed in this study differ from those produced by injection of other polyanionic substances but their precise pathogenesis is still uncertain.

23. Reticuloendothelial phagocytic response to bacterial challenge after traumatic shock. J. E. Kaplan, W. A. Scovill, H. Bernard, T. M. Saba, and V. Gray. Circ. Shock 4: 1-12, 1977.

Resistance to intravenous (IV) and intraperitoneal (IP) bacterial challenge during periods of reticuloendothelial (RE) depression following trauma as well as the influence of bacteremia on RE phagocytosis were studied. The experimental shock model utilized was the anesthetized (2 mg/100 g sodium pentobarbital) male rat subjected to nonlethal Noble-Collip drum trauma. During post-traumatic RE depression (60 min after injury) rats were challenged IV or IP with Escherichia coli (1.02×10^{10}). The clearance half-time of the bacterial load injected intravenously in controls was 1.23 ± 0.10 min. In contrast, the half-time was 3.62 ± 0.69 min after sublethal trauma ($p<0.005$) and associated with prolonged blood bacterial retention. Pulmonary localization of E. coli administered either IV or IP was elevated in traumatized rats. Comparison of routes of bacterial challenge with respect to blood levels of viable bacteria suggested lower host bacterial resistance to the IP injection

as opposed to the IV route of administration. Production of experimental bacteremia in normal rats resulted in a 39% depression ($p<0.01$) of RE test colloid clearance rate accompanied by a 49% increase ($p<0.01$) in pulmonary colloid localization. The data suggest that depressed systemic RE clearance capacity following trauma may decrease systemic resistance to septicemia, and that severe bacteremia may further undermine the functional state of the reticuloendothelial system.

24. Thermal trauma: Therapeutic achievements and investigative horizons. J. R. Lloyd. Surg. Clin. N. A. 57: 121-138, 1977.

No summary available.
Key topics discussed: wound infection and sepsis, burn hypermetabolism, and therapies.

25. The effect of methylprednisolone on leukocyte function. E. D. Renner, M. L. Webel, and R. E. Ritts, Jr. J. Reticuloendo. Soc. 14: 530-537, 1973.

In order to assess the in vivo effects of large single doses of corticosteroid on the phagocytosis and intracellular killing of bacteria by leukocytes, we administered to human volunteers 500 mg of methylprednisolone by intravenous injection. We assayed the subjects' whole blood and isolated granulocytes to determine their ability to phagocytize and kill Staphylococcus aureus (strain 502A) before and at 4 and 24 hr after the drug was given.

The effect of a single 500-mg dose of methylprednisolone on the antimicrobial system of leukocytes was evaluated. Three subjects were given the drug intravenously, and their granulocyte phagocytosis, total granulocyte count, and plasma corticosteroid level were measured at 4 and 24 hr later. Methylprednisolone did not alter the intrinsic phagocytosis or the intracellular killing capacities of the granulocytes, and the presence of the drug in plasma had no effect on these functions of the granulocyte or on the serum factors necessary for these functions.

It has been reported that leukocyte migration is diminished by steroids--an effect that could influence the in vivo phagocytic ability of leukocytes, although we could not assay for this effect by our methods, we believe that it must be considered in evaluating the long-term effect of corticosteroid therapy.

26. Dialysis, neutropenia, lung dysfunction and complement. P. A. Chervenick. New Engl. J. Med. 296: 810-812, 1977.

Although it seems clear that complement is responsible for the neutropenia and leukostasis, it is not clear whether complement has additional roles in neutrophil regulation, such as regulating the release from bone marrow, or in neutrophil production. Its role in chemotaxis is well known. That complement may have an additional role in regulation of neutrophils is indicated by studies of Rother, who demonstrated that C3 results in increased mobilization of neutrophils from an isolated perfused bone in vitro and that after injection in vivo, leukocytosis occurred. These findings are very similar to those observed with endotoxin. After endotoxin injection substances appear in serum that cause the release of neutrophils from the marrow to the blood (neutrophil-releasing factor), and also stimulate the production of neutrophils in vitro

(colony-stimulating activity). It is quite possible that both these effects are mediated in some manner by one or more components of the complement system.

Complement has been implicated in many areas of clinical medicine, with effects being both beneficial and detrimental. It is probably best known as an agent that causes lysis of sensitized microbes and erythrocytes. Perhaps its most important function is in host defense against pathogenic organisms through its opsinization of bacteria and enhancement of phagocytosis. Other biologic functions of complement include its role in immune adherence, chemotaxis, the inflammatory response, blood clotting and destruction of malignant cells.

27. Cellular immunity after intravenous administration of methylprednisolone. M. L. Webel, R. E. Ritts, Jr., H. F. Taswell, J. V. Donadio, Jr., and J. E. Woods. J. Lab. Clin. Med. 83: 383-392, 1974.

This paper describes attempts to ascertain the mechanism of this type of corticosteroid regimen by studying several immune functions of leukocytes after a single intravenous dose of methylprednisolone.

Normal volunteer subjects were given various doses (80, 250, 500 or 1000 mg) of methylprednisolone intravenously and blood samples were taken at various intervals afterward. Lymphoblastic transformation in response to phytohemagglutinin stimulation and allogeneic cells was markedly suppressed. This response may be related to suppression of transplant-antigen-stimulated lymphoblastic transformation involved in renal allograft rejection. Phagocytosis of latex particles and bacteria and intracellular killing by peripheral leukocytes were unimpaired. There was a profound peripheral lymphopenia concomitant with an increased neutrophil count within the first 24 hours after administration of the dose. The combination of these effects fulfills most requirements for an agent useful in treating acute graft rejection. No alteration of total complement levels was observed.

28. Corticosteroid effect on phagocytosis and NBT reduction by human polymorphonuclear neutrophils. J. H. Chretien and V. F. Garagusi. J. Reticuloendo. Soc. 11: 358-367,1972.

The polymorphonuclear neutrophils (PMNs) from 10 patients receiving prednisone, dexamethasone, or hydrocortisone sodium succinate were found capable of normal phagocytosis of latex particles when compared with cells from unmedicated control subjects. However, nitroblue tetrazolium (NBT) reduction was impaired in the cells of steroid-treated patients. Neutrophils from normal volunteers steroid treated in vitro with 5 µg/ml of hydrocortisone produced the normal latex phagocytosis together with impaired NBT reduction. However, more than 20 times this concentration of hydrocortisone sodium succinate was required in vitro to impair NBT reduction. It is concluded that corticosteroid therapy does not alter engulfment by the human neutrophil, but does interfere with NBT reduction and probably intracellular killing.

29. Fatal septicemia due to nonpigmented Serratia marcescens. G. J. Wise, L. E. Jacobson, E. Bottone, S. S. Schneierson, and H. Brendler. N. Y. St. J. Med. 70: 564-567, 1972.

Until recently, the nonpigmented form of S. marcescens has been considered a non-pathogenic organism. This report describes 2 deaths from septicemia due to this organism. Both infections occurred in debilitated patients.

The resistance of this organism to most antibiotic agents, as demonstrated by in vitro sensitivity studies and lack of clinical response, emphasizes its virulence.

30. Gram-negative endotoxin shock due to Serratia marcescens. J. N. Henry, E. W. Gelfand, and E. J. Hinchey. Canad. Med. Assn. J. 102: 45-48, 1970.

Shock associated with sepsis has been recognized for many years, having been described first by Laennec in 1831. Gram-negative septicemia with peripheral vascular collapse, although possibly recognized earlier, was first reported in 1951 by Waisbren, who described his clinical observations on 29 patients with gram-negative bacteremia, of whom 15 had associated hypotension. In this report, the successful management of a patient with gram-negative endotoxin shock due to pigmented Serratia marcescens, an organism infrequently reported as a cause of this syndrome, is described.

31. The mechanism of action of a single dose of methylprednisolone on acute inflammation in vivo. S. L. Wiener, R. Wiener, M. Urivetzky, S. Shafer, H. D. Isenberg, C. Janov, and E. Meilman. J. Clin. Invest. 56: 679-689, 1975.

A model system for the study of inflammation in vivo has been developed using the 16-h polyvinyl sponge implant in the rat. This system allows for simultaneous measurement of in vivo chemotaxis, volume of fluid influx, and fluid concentrations of lysosomal and lactic dehydrogenase (LDH) enzymes. In addition, the enzyme content of inflammatory fluid neutrophils may also be determined. A parallel time course of neutrophil and lysosomal enzyme influx into sponge implants was observed. This was characterized by an initial lag phase and a rapid increase between 5 and 16 h.

Large intravascular doses of methylprednisolone markedly inhibited neutrophil influx into sponges and adjacent connective tissue. Secondary to decreased neutrophil influx, fewer neutrophils were available for lysis, and lysosomal enzyme levels in inflammatory fluid decreased. No evidence for intracellular or extracellular stabilization of neutrophil lysosomal granules by methylprednisolone was found.

32. Mechanism of anti-complementary activity of corticosteroids in vivo: Possible relevance in endotoxin shock. J. T. O'Flaherty, P. R. Craddock, and H. S. Jacob. Proc. Soc. Exptl. Biol. Med. 154: 206-209, 1977.

Corticosteroids protect animals from potentially lethal doses of endotoxin, but the mechanism for this protection remains as controversial as the mechanism for the toxicity of endotoxin itself. Recent evidence suggests that complement activation may be involved.

The effects of several corticosteroids on the sudden neutropenia which occurs in animals exposed to activated complement components were studied. Solu-Medrol and Solu-Cortef in high concentrations inhibited such neutropenia but only if present before or during the period of complement activation; Decadron was much less efficient. The observed dose and temporal relationships are strikingly similar to those noted in previous studies of corticosteroid protection from endotoxin shock, suggesting that complement-mediated alterations in neutrophils may be critical in this entity.

33. Adrenergic mechanisms in the hepatic arterial circulation of baboons. K. G. Swan, J. C. Kerr, C. B. Wright, and D. G. Reynolds. Surgery 81: 326-334, 1977.

The effects of intra-arterial injections and infusions of three adrenergic amines upon hepatic arterial blood flow were measured in anesthetized baboons before and after alpha and beta adrenergic blockade with intravenous phenoxybenzamine and propranolol. Injections of norepinephrine or epinephrine caused dose-dependent decreases in hepatic arterial blood flow. These responses were attenuated by alpha adrenergic blockade and were unchanged by beta adrenergic blockade. Injections of isoproterenol caused dose-dependent increases in hepatic arterial flow. These increases were relatively small and were reversed to constriction at low doses and attenuated at high doses of the agonist by beta adrenergic blockade. Intrahepatic arterial infusions of constrictors were unaccompanied by autoregulatory escape. The degree of constriction was attenuated by alpha adrenergic blockade but was not potentiated by beta adrenergic blockade. Intrahepatic arterial infusion of a relatively large dose of isoproterenol was required to evoke a relatively modest, but sustained, increase in hepatic arterial blood flow. This response was not potentiated by alpha adrenergic antagonism, but was attenuated by beta adrenergic blockade. These observations suggest an apparent and relative decrease in beta adrenergic receptor activity in the hepatic arterial bed of the baboon when compared to other regional circulations such as the mesenteric and femoral beds. These beta receptors are relatively resistant to both stimulation and blockade.

34. Role of intraintestinal endotoxin in death from peritonitis. P. Cuevas and J. Fine. Surg. Gynec. Obstet. 134: 953-957, 1972.

Septic peritonitis, produced by an intraperitoneal injection of intestinal contents or an 18 hour culture of pathogenic Escherichia coli fortified with hemoglobin, produced an endotoxemia as early as 90 minutes after the injection. The titer of endotoxin in the peritoneal fluid was 4-8 times greater than in plasma. Removal of the bacteria from the injected fluids just prior to injection delayed the onset of the endotoxemia and reduced the titer of endotoxin in the peritoneal fluid and the plasma but did not prevent shock and death. Chemical or nonseptic peritonitis produced by bile, gastric juice, or pancreatic extract injected intraperitoneally in a dose of 5 ml/kg of body weight evoked an endotoxemia at different intervals, depending on the irritating properties of these substances. Gastric juice produced the highest titer of circulating endotoxin obtained in the study and caused death within three hours. Bacteria from the intestinal canal were recovered from the peritoneal fluid in nonseptic peritonitis 3-4 hours after onset, but they were far too few to account for the amount of endotoxin found in the peritoneal fluid at that time. The mortality rate was 100% in nonseptic as well as in septic peritonitis, but the survival time in nonseptic peritonitis, except in the instance of gastric juice, varied from 10-18 hours as compared with 7 hours in the instance of bacterial peritonitis.

Kanamycin injected directly in the intestine prior to the onset of bacterial peritonitis reduced the endotoxin titer in blood to, or near, zero, and in the peritoneal fluid, to less than half of that in the untreated rabbit,

and reduced the mortality rate to 50%. On the other hand, prophylactic intramuscularly administered kanamycin, which eliminated the injected bacteria by the fourth hour, did not reduce the endotoxin titers in plasma or peritoneal fluid and did not reduce the mortality rate.

These data demonstrate that circulating endotoxin in septic and nonseptic peritonitis is derived largely from the intestinal canal, and, therefore, that appropriate therapy for shock caused by these disorders should include suppression of the intra-intestinal flora in addition to elimination of the irratating intraperitoneal fluid. The effectiveness of therapy can be gaged by serial monitoring of the plasma and peritoneal fluid for endotoxin.

35. The effect of glucose infusion on myocardial performance during acute hypoxia. G. B. H. Lewis and K. Prasad. Japan. Heart J. 18: 102-111, 1977.

The effects of hypoxia with or without glucose infusion on the cardiac contractility, blood pressure, electrocardiogram, blood electrolytes (sodium and potassium), glucose, pH, pO_2, and pCO_2 in anesthetized dogs were studied. Hypoxia was induced by ventilating the dogs with reduced oxygen (10%) in the inspired air. Hypoxia produced a decrease in the cardiac contractility and blood pressure, and an increase in the heart rate and central venous pressure. It produced a decrease in the blood pH, pO_2, and pCO_2, and an increase in the blood glucose and potassium. Glucose infusion during hypoxia delayed the rate of decrease in the contractility and blood pressure significantly. The time for decrease in the contractility to 45 to 50% was increased by 67%. Glucose infusion prevented the loss of potassium from the cell. Glucose infusion however was unable to correct acidosis. These results indicate that glucose infusion during hypoxia might prevent or delay the deterioration of myocardial function.

36. Quantitative phagocytosis by human polymorphonuclear leucocytes. Use of radiolabelled emulsions to measure the rate of phagocytosis. A. Forsgren, D. Schmeling, and O. Zettervall. Immunology 32: 491-497, 1977.

A new micro-method for the quantitative measurement of phagocytosis by neutrophils is described. The material used for phagocytosis consists of a radioactive oil emulsion coated with E. coli lipopolysaccharide. Uptake of radioactive material is a function of cell number, duration of incubation, dilution of serum used for opsonization, content of lipopolysaccharide and concentration of emulsion. This method can be used to quantify rapidly and precisely phagocytosis rates of as few as 5×10^4-10^6 polymorphonuclear leucocytes and the opsonic activity of 10 µl serum.

37. Humoral factor depletion and reticuloendothelial depression during hemorrhagic shock. D. J. Loegering. Am. J. Physiol. 232: H283-287, 1977.

Circulating opsonic activity and reticuloendothelial system (RES) phagocytic function were determined in anesthetized rats subjected to hemorrhagic shock. Animals were hemorrhaged to and maintained at 40 mmHg arterial blood pressure until they spontaneously took back 5% or 40% of the maximum bled volume. The phagocytic index, as determined by colloid clearance kinetics, was decreased in both groups following reinfusion of

the shed blood. The reduction in phagocytic index was associated with decreased liver, unchanged spleen, and increased lung test colloid localization. Plasma opsonic activity, as determined by liver slice bioassay, was decreased 50-60% at 5% and 40% uptake of the maximum shed volume, decreased further 15 min after reinfusion in both groups, and tended to recover 1 h after reinfusion in the 5% uptake group. In vitro hepatic phagocytic activity of liver slices from shocked animals in the presence of normal rat plasma was decreased only in the 40% uptake animals after reinfusion when the arterial blood pressure had decreased to 50 mmHg. These data indicate that the depression of RES phagocytic function during hemorrhagic shock is associated with and may be mediated, in part, by decreased circulating opsonic activity.

38. The effect of endotoxin on the mast cell c'AMP system. F. L. Glauser, J. Palmer, S. Cecconi, W. Schoolcraft, I. Wells, H. Novey, P. Egan and D. Smeltzer. Ann. Allergy 38: 104-106, 1977.

Endotoxin leads to release of mast cell substances in both human spontaneous and animal experimental models. There is some evidence that this release may, as in asthma, be immunologically mediated. Whether this release is cytotoxic (destructive) or noncytotoxic (enzyme mediated as in asthma) has not, to our knowledge, been investigated. This study attempts to define the pathway or pathways leading to endotoxin-serum (ET-S) induced histamine release in the isolated peritoneal mast cells of hamsters.

To determine whether the endotoxin induced release of histamine is mediated via the mast cell c'AMP system, hamster mast cells were isolated and incubated (prior to endotoxin-serum stimulation) with disodium cromoglycate, isoproterenol and aminophylline. All drugs caused significant inhibition of the ET-S histamine release.

It is concluded that (1) in vitro, endotoxin with the addition of serum causes histamine release from hamster mast cells, (2) the ET-S mixture releases histamine by decreasing c'AMP levels and (3) the ET-S complex may attach to the cholinergic receptor. Whether additional receptors are also employed is not answered by this study.

39. Blood flow in rats during hemorrhagic shock: Differences between surviving and dying animals. J. Blahitka and K. Rakusan. Circ. Shock 4: 79-93, 1977.

Cardiac output distribution was measured during hemorrhage and hemorrhagic shock in unanesthetized rats. In comparison to control animals, a varying degree of decreased blood flow was found in the skin, kidneys, splanchnic bed, and carcass. Bronchial and hepatic arterial blood flows were within normal limits for the entire experiment. Whereas the coronary blood flow fluctuated between values higher and lower than normal, the cerebral blood flow values were normal or decreased. When survivors were compared to dying rats, differences were found in the early and late stages of shock. Initially, the carcass flow in survivors was higher, while the splanchnic flow was lower, than in dying rats. This redistribution of cardiac output may be responsible for an increased venous return and improved chances for survival. At the late stages of shock, survivors had significantly higher bronchial and hepatic arterial blood flow.

40. Metabolic effects of experimental bacteremia. J. Postel and P. R. Schloerb. Ann. Surg. 185: 475-480, 1977.

Current understanding of gram-negative sepsis suggests that organ failure with subsequent death may ultimately be related to failure of high energy metabolism. Since glucose is a major component of the energy reservoir, numerous studies have focused on the significance of carbohydrate metabolism during systemic infections.

Hemodynamic and metabolic effects of a lethal 5-hour infusion of Ps. aeruginosa at a dose of 10^8 organisms/ml/min were studied in 39 dogs. Blood glucose, insulin, catecholamines, body temperature, WBC, and hemodynamic parameters were measured before and at 1-hr intervals during controlled bacterial infusions. Induced bacteremia in the upper 10^4 range per ml of blood was accompanied by a decline of mean arterial blood pressure from 130±6 mmHg to 84±12 mmHg at 4 hrs, hypothermia, leukopenia, and hypoglycemia. Death within 24 hrs was associated with hypoinsulinemia and increased blood catecholamines. Survival was characterized by maintenance of arterial blood pressure, only moderate decline in blood glucose elvels, and normal plasma insulin concentrations with little change in plasma catecholamines. Mortality could be reduced significantly by glucose administration. This was associated with correction of hypoglycemia, rise in plasma insulin activity and increased energy production.

41. Tissue factor generation by human mononuclear cells: Effects of endotoxin and dissociation of tissue factor generation from mitogenic response. F. R. Rickles, J. Levin, J. A. Hardin, C. F. Barr, and M. E. Conrad, Jr. J. Lab. Clin. Med. 29: 792-803, 1977.

The effects of the presence of endotoxin in a mononuclear cell culture system have been assessed. Endotoxin was shown to be mitogenic for human peripheral blood lymphocytes and capable of stimulating the generation of tissue factor. Concentrations of endotoxin, found to contaminate many commercial mitogens and antigens, activated mononuclear cells in a time-dependent manner. Generation of tissue factor was detected in cultures harvested from 2 to 72 hrs following stimulation with endotoxin. Dose-response curves relating concentrations of endotoxin to mononuclear cell stimulation were determined; as little as 0.001 µg/ml of E. coli endotoxin was capable of stimulating the generation of tissue factor in the cell cultures. The mitogenic effect of endotoxin was modest, however, and appeared to be unrelated to the ability of endotoxin to activate tissue factor. Inhibition of DNA synthesis in the cell cultures by cytosine arabinoside or nonlethal irradiation failed to impair the generation of tissue factor. Endotoxin contamination of various reagents used in cell culture was evaluated with the Limulus assay, which detected as little as 1×10^{-4} µg/ml of endotoxin. Endotoxin was detected in preparations of phytohemagglutin, purified protein derivative of the tubercle bacillus, mumps vaccine, tetanus toxoid, concanavalin A, and pokeweed mitogen. Because of the broad implications of contamination by endotoxin of various reagents, we assessed the specificity of the Limulus assay for the detection of endotoxin in the lectin, concanavalin A, and determined that the reaction was specific for endotoxin. Contamination by endotoxin of mononuclear cell culture systems should be considered as a possible factor in the production of various biological effects attributed to some commonly used mitogens and antigens.

42. Cardiopulmonary effects of volume loading in patients in septic shock. M. M. Krausz, A. Perel, D. Eimerl, and S. Cotev. Ann. Surg. 185: 429-434, 1977.

The effect of volume loading in 20 patients with clinical and bacteriological evidence of generalized sepsis was studied. The patients were divided into two groups according to their response to volume loading. Group A included 9 patients in whom the initial pulmonary capillary wedge pressure (PWP) was lower than the central venous pressure (CVP). In this group the intravenous administration of 5089±409 ml/24 hr fluids was accompanied by a significant rise in blood pressure from 94.4±9.3 mmHg to 118.9±6.3 mmHg with no significant change in pulse rate or CVP. PWP rose from 5.7±1.8 to 10.0±1.4. The rise in cardiac output from 8.0±1.3 liter/min to 9.7±1.1 liter/min was not statistically sigificant. Group B included 11 patients in whom the initial PWP was higher than the CVP. In this group, signs of fluid overloading appeared after administration of 3151±540 ml/24 hr. There was no significant change in blood pressure, pulse rate, CVP, PWP or cardiac output. Urine output was adequate in both groups. This volume load did not affect pulmonary oxygenating capacity (PaO_2/F_1O_2) and effective lung compliance in both groups, but the maintenance of an unchanged oxygenating capacity necessitated an increase in PEEP in some patients. Thus, synchronous monitoring of PWP and CVP in septic shock is helpful in selecting patients (Group A) who will best respond to fluid loading without deterioration of pulmonary oxygenating capacity. PEEP ventilation may be necessary in some patients to maintain the favorable effect of volume loading.

43. Contraction and resting stiffness of isolated cardiac muscle: effects of inotropic agents. K. Taubert, J. T. Willerson, W. Shapiro, and G. H. Templeton. Am. J. Physiol. 232: H275-282, 1977.

The purpose of this study was to test the hypothesis that either hypoxia and its combined effects with extracellular calcium (Ca), digoxin, and ouabain, or these positive inotropic agents acting alone or in combination, influence contraction and resting stiffness of isolated papillary muscle. Stiffness was measured utilizing the sinusoidal forcing function technique. Neither an increase in extracellular calcium concentration (from 2.5 to 4.0 mM) nor digoxin or ouabain in either Ca concentration altered contraction or resting stiffness in the well-oxygenated environment. Resting stiffness for any given resting tension was increased at the end of hypoxia only in the presence of digoxin, and this occurred in both 2.5 mM Ca ($P<0.02$) and in 4.0 mM Ca ($P=0.05$). Contraction stiffness for any given tension was increased in 2.5 mM Ca by hypoxia alone ($P<0.05$) and by hypoxia in the presence of digoxin ($P<0.005$) and ouabain ($P<0.02$), but was not increased in any experiments conducted in 4.0 mM Ca. The conclusions from these data are that certain experimental conditions of the study evoked different directional changes in stiffness and contractility. Further, changes in contraction stiffness are not always paralleled by changes in resting stiffness.

44. Instantaneous force-velocity-length relations in isolated dog heart. K. T. Weber and J. S. Janicki. Am. J. Physiol. 232: H241-249, 1977.

The mechanics of left ventricular contraction were investigated in terms of instantaneous mural force, mid-wall circumferential fiber shortening velocity (dL/dt), and fiber length (L) in seven servo-regulated hearts.

The steady-state response of a series of variably preloaded or afterloaded allasotonic contractions were utilized. Norepinephrine (0.55-1.38 μg/min) or propranolol (0.07-0.14 mg/min) were given to alter inotropic background. For any given contractile state and initial L, maximum dL/dt was not attained instantly but after a finite time of ejection (39 ms±0.2 SE; range, 24-60) and from a lesser length (92%±0.5 SE; range 83-99) than present at end diastole. Beyond this initial period instantaneous dL/dt was dependent on both instantaneous force and length while independent of time after contraction and initial L. Instantaneous dL/dt also varied with contractile state, e.g., dL/dt was less after propranolol and greater after norepinephrine. Peak dL/dt for all conditions was a function of the extent of shortening (r=0.90). Thus, the trajectory describing instantaneous force, velocity, and length provides a useful description of both the mechanical behavior and contractile state of the ventricular myocardium.

45. Pulmonary perfusion and gas exchange in hemorrhage and shock. A. B. Malik and J. C. Newell. J. Appl. Physiol. 42: 279-286, 1977.

Pulmonary perfusion and gas exchange were studied during control period, maximum bled volume (MBV), posttransfusion (PT), and circulatory decompensation (CD) in anesthetized, supine, spontaneously breathing dogs. Pulmonary arterial pressure (Pa) did not change from control during MBV and pulmonary venous pressure decreased. The maintenance of Pa was associated with development of metabolic acidosis. Pa increased above control during PT and returned toward control during CD. The gravity-dependent regional pulmonary perfusion measured with labeled microspheres did not change from control during MBV. Regional perfusion became more uniform during PT and returned toward control during CD. Venous admixture ($\dot{Q}s/\dot{Q}t$) increased from 9.4±2.3 to 20.5±4.6%, alveolar-arterial PO_2 gradient (PA_{O2}-Pa_{O2}) increased from 20.1±7.5 to 45.7±7.1 torr, and dead space (V_D) increased from 87.3±5.2 to 104.2±3.9 ml during MBV. These values returned toward control during PT and remained unchanged during CD. The wet-dry lung weight ratios were normal at CD and there was no histological evidence of embolization, atelectasis, and edema. The normal distribution of regional pulmonary perfusion during MBV may be secondary to the acidosis-induced maintenance of Pa at control levels. The shift in perfusion during PT may be due to elevated Pa, and the normal distribution of perfusion during CD may be due to return in Pa to control. The increases in $\dot{Q}s/\dot{Q}t$, PA_{O2}-Pa_{O2}, and V_D at MBV suggest ventilation-perfusion inequalities. The mechanisms for these changes may be related to the development of atelectasis, thromboembolization, and edema during MBV. The return in $\dot{Q}s/\dot{Q}t$, PA_{O2}-Pa_{O2}, and V_D toward control following transfusion suggests that regional ventilation and perfusion are better matched during PT and CD than during MBV, and that mechanisms underlying the alterations are partially reversible following transfusion.

46. Neonatal sepsis at The Johns Hopkins Hospital, 1969-1975: Bacterial isolates and clinical correlates. F. J. Crosson, Jr., H. M. Feder, Jr., J. A. Bocchini, Jr., J. M. Hackell, and J. G. Hackell. Johns Hopkins Med. J. 140: 37-41, 1977.

The experience with neonatal sepsis at The Johns Hopkins Hospital during 1969-1975 was reviewed. Major pathogens included Escherichia coli, Group B streptococcus, other streptococci, and Klebsiella. Nineteen percent of coliform isolates were kanamycin-resistant. The frequency of recovery of E. coli was increased in early-onset sepsis, and the frequency of

recovery of Klebsiella was increased in late-onset sepsis. The mortality rate was 23%. The frequency of recovery of E. coli was increased in fatal cases, and mortality was highly correlated with the presence of gastrointestinal catastrophe. Ampicillin and gentamicin are the initial antibiotics of choice for neonatal sepsis at this institution; a penicillinase-resistant penicillin should be added when Staphylococcus aureus involvement is likely, and addition of chloramphenicol or clindamycin should be considered for infants at increased risk for Bacteroides fragilis sepsis.

47. Prostaglandins and the control of blood flow in the canine myocardium. T. H. Hintze and G. Kaley. Circ. Res. 40: 313-320, 1977.

A comprehensive study was undertaken to evaluate the effects of inhibition of prostaglandin (PG) synthesis on a variety of reactions in the coronary vascular bed of anesthetized, open-chest dogs. In 23 dogs an electromagnetic flow probe (EMFP) and hydraulic occluder were placed around either the left anterior descending or circumflex branches of the coronary artery and a needle was inserted distal to the EMFP. Injections into the coronary artery of arachidonic acid (AA), bradykinin, adenosine, angiotensin, and PGE_2 were given before and after inhibition of PG synthesis by indomethacin (IND) or meclofenamate (MF). The effects of the inhibitors on reactive hyperemia resulting from 5-, 10-, 15-, and 20-second occlusions and the dilation resulting from 90-second exposure to 8% O_2 were also examined. In each experiment, inhibition of PG synthesis was ascertained by the elimination of vasodilation to AA. After administration of IND or MF, while baseline coronary blood flow was slightly reduced, the total increment of blood flow to vasodilator agents was not significantly altered. Whereas the peak dilation and volume of reactive hyperemia were decreased, the percent flow debt repaid was unchanged and total increment of coronary flow due to hypoxia-induced vasodilation was not significantly modified. Vasoconstrictor responses to angiotensin were also unchanged. These results indicate that while inhibitors of PG synthesis increase coronary resistance, they do not adversely affect vascular responsiveness. We conclude that prostaglandins play little, if any, role in modulating coronary blood flow.

48. Mechanical and metabolic effects of insulin on newborn lamb myocardium. S. E. Downing, J. C. Lee, and R. P. Rieker. Am. J. Obstet. Gynec. 127: 649-656, 1977.

The effects of insulin on myocardial contractility (MC) and metabolism were studied in 18 newborn lambs. Cardiac work and rate were kept constant. Following insulin (80 units, intravenously), contractility increased and remained elevated for 1 hr. This was not prevented by beta blockade or glucose infusion. Myocardial extraction and uptake of glucose and nonesterified fatty acid (NEFA) increased, the arterial concentration of both decreased. But after glucose fell to less than 20% of control, uptake of both glucose and NEFA declined as did MC. It is concluded that in the neonate insulin increases MC as well as substrate uptake.

49. Biological activities of tritiated endotoxins: correlation of the Limulus lysate assay with rabbit pyrogen and complement-activation assays for endotoxin. P. A. Tomasulo, J. Levin, P. A. Murphy, and J. A. Winkelstein. J. Lab. Clin. Med. 89: 308-315, 1977.

Endotoxin is an integral part of the cell wall of gram-negative bacteria and is capable of producing a variety of biological effects. Preparations of radiolabeled endotoxin are potentially useful for studies of the biological interactions of endotoxin. Tritiated endotoxin has been prepared by three different methods and been shown to be biologically active, as measured by the Limulus lysate assay (LLA) for endotoxin. However, in order to demonstrate whether these labeled endotoxins had been altered significantly by the techniques used to introduce the tritium, it was necessary to evaluate them in other assays which measured different biological effects of endotoxin.

Tritiated endotoxins were prepared by three different methods. The biological activities of the tritiated endotoxins were determined by the Limulus amebocyte lysate assay, a rabbit pyrogen assay, and a complement-activation assay and were compared to native, unlabeled endotoxin. All three tritiated endotoxin preparations manifested adequate biological activity in each of the three assay systems, and all three assays ranked the biological activities of the different endotoxin preparations in the same order. Endotoxin tritiated by the Wilzbach procedure retained most of its biological activity and also had the highest specific radioactivity. The good correlation between the Limulus lysate, rabbit pyrogen, and complement-activation assays suggests that the same active site of the endotoxin molecule is identified by the three different assays.

50. In vivo and in vitro effect of bacterial endotoxin on erythroid precursors (CFU-E and ERC) in the bone marrow of mice. K. B. Udupa and K. R. Reissmann. J. Lab. Clin. Med. 89: 278-284, 1977.

Erythropoietin injection raised within 24 hr the number of CFU-E in the femoral marrow of polycythermic mice by 837%. Endotoxin given at 0 to 24 hr before erythropoietin nearly abolished this CFU-E increase. Endotoxin in the culture medium did not inhibit erythroid colony formation, but in vivo endotoxin suppressed erythropoietin-induced differentiation of proerythroblasts from their precursors. Endotoxin thus suppresses marrow erythropoiesis either by inhibiting transformation of erythroid precursors into CFU-E or by causing the disappearance, perhaps by emigration, of CFU-E from the marrow.

51. Phagocytic and metabolic parameters of alveolar macrophages after sublethal traumatic shock. P. W. Gudewicz, T. M. Saba, and F. Coulston. Circ. Shock 3: 337-343, 1976.

Select aspects of glucose metabolism and glucose transport were investigated in vitro in rat alveolar macrophages (AM) after a sublethal Noble-Collip drum traumatic shock procedure. Phagocytosis of Pseudomonas aeruginosa was stimulated in macrophages acutely after traumatic injury. O_2 consumption was significantly elevated during bacterial phagocytosis. $^{14}CO_2$ production from [1-^{14}C] glucose was stimulated 400% in controls and 450% after traumatic shock in macrophages during bacterial phagocytosis. Phagocytosis resulted

in a significant increase in the uptake of 2-deoxy-D-glucose (2-DG) by control AM whereas 2-DG transport was not augmented during phagocytosis after traumatic shock. These results provide a metabolic basis for the alterations in alveolar macrophage function after whole-body traumatic injury and further suggests that alterations in macrophage membrane permeability to glucose may be an important metabolic lesion in macrophages after shock or injury.

52. Metabolic effects of glucose-insulin-potassium infusion during experimental intraperitoneal sepsis. N. T. Ryan and G. H. A. Clowes, Jr. Circ. Shock 3: 309-313, 1976.

Control fasted and septic fasted rats were given either saline or glucose-insulin-potassium (GIK) infusions to evaluate the metabolic response of heart, muscle, and adipose tissues. GIK resulted in an elevation of heart and adipose tissue pyruvate dehydrogenase (PDH) activity in both control fasted and septic fasted animals, when compared with saline-infused controls. This response was accompanied by a reduction in circulating fatty acid levels in GIK-infused groups. In contrast, diaphragm PDH failed to increase after GIK administration to the septic animals, but did increase after GIK in the control fasted group.

In the saline-infused groups, heart and adipose tissue PDH activities were higher (almost 2-fold) and fatty acids lower (almost one-half) in the septic fasted than in the control fasted animals, whereas diaphragm PDH was essentially the same in both groups.

These data suggest insulin resistance in diaphragm, but not in heart or adipose tissue during intra-abdominal sepsis, and provide new, direct evidence for a metabolic response to GIK by heart. These changes may contribute to the cardiovascular effects of GIK infusion during sepsis.

53. Indomethacin protection in traumatic shock. S. Halevy and B. M. Altura. Circ. Shock 3: 299-302, 1976.

Pretreatment of mice with different dose-duration regimens of a prostaglandin (PG) synthetase inhibitor, indomethacin, exerted significant early protection (i.e., up to 2 hr) after Noble-Collip drum trauma (NCDT). Indomethacin pretreatment did not, however, improve long term survival after NCDT. These results suggest that synthesis and release of PG compounds early in trauma may contribute to the high incidence of early mortality seen after NCDT. Our data support the notions that: 1) PG molecules may indeed play a role in circulatory shock; and 2) PG synthetase inhibitors may be useful as an adjunct therapy in trauma.

54. Insulin secretion and the carbohydrate metabolic alterations of endotoxemia. B. J. Buchanan and J. P. Filkins. Circ. Shock 3: 267-280, 1976.

The role of endogenous hyperinsulinemia in the pathogenesis of the altered carbohydrate homeostasis of endotoxin shock was investigated in male Holtzman rats. Endotoxin (1 mg iv) resulted in an early hyperglycemia and a concomitant elevation of serum insulin. Glucose tolerance tests (400 mg of D-glucose

ip) 2 hrs after endotoxin showed no alterations despite an exaggerated insulin response. By 4-5 hrs endotoxemic rats were hypoglycemic and depleted of liver glycogen. Endotoxemia depressed both in vivo gluconeogenesis and glycogensis from alanine. Total body glucose oxidation, as assessed by the recovery of ^{14}CO from either a tracer dose or 400 mg of glucose ip, was enhanced by endotoxin. No alterations in glucose oxidation incident to endotoxemia occurred in rats rendered insulinopenic by either mannoheptulose or streptozotocin. The data suggest that hyperinsulinemia mediates the carbohydrate depletion and subsequent hypoglycemia accompanying endotoxin shock in rats.

55. Variations in plasma levels of adenosine 3',5'-monophosphate during clinical sepsis. W. J. Sibbald, V. M. Sardesai, A. Short, and R. F. Wilson. Surg. Gynec. Obstet. 144: 199-204, 1977.

Plasma levels of adenosine 3',5'-monophosphate were measured in 43 patients with bacterial infections of varying degrees of severity. The most severely ill patients, who died within 48 hrs of study, had the highest levels of plasma adenosine 3',5'-monophosphate, 38.4±29.8 picomoles per ml. A significant and progressive decrease in plasma adenosine 3',5'-monophosphate level toward normal was found with lesser degrees of sepsis. However, even those patients who survived exhibited elevations of plasma adenosine 3',5'-monophosphate levels, 12.9±5.4 picomoles per ml, significantly above normal. Shock and impaired renal function appeared to contribute to the elevated levels found in the most severely ill patients. In those less severely ill, with normal renal function and no shock, the plasma adenosine 3',5'-monophosphate level was still significantly elevated above normal, suggesting that severe bacterial infection itself contributes to the generation of elevated plasma adenosine 3',5'-monophosphate levels. Various hormonal changes or increased cellular permeability, or both, may account for some of the increase of this intracellular nucleotide in the plasma. It is suggested that extremely high levels of plasma adenosine 3',5'-monophosphate are indicative of a poor prognosis.

56. Evaluation of the possible role of serum factors in the clearance of endotoxin from the blood. H. Gans and G. Wendell. J. Surg. Res. 21: 415-424, 1976.

Evidence that gram-negative organisms of enteric origin or the endotoxins derived from them play a significant role in the number of clinical conditions continues to accumulate. Thus, their possible contribution to expermental and clinical liver failure is suggested. It has been found that endotoxins, once they traverse the gutwall, escape equally readily into portal vein blood as into the intestinal lymphatics. Where endotoxin leaving via the former route is readily eliminated and detoxified by a normal liver, that which enters the lymphatics also homes in on the liver; systemic endotoxins are predominantly eliminated by the Kupffer cells.

The clearance of endotoxin by macrophages, or its phagocytosis, far from being the only one present to reverse the adverse in vivo effects of endotoxin, has been the process that so far has received the most attention because it is the easiest one to study.

Animals can be rendered tolerant or refractory to endotoxin, a condition characterized by a diminished response to endotoxin, particularly to its lethality and pyrogenicity, and these animals exhibit enhanced blood clearance rates.

Circulating endotoxins are eliminiated from the blood by phagocytes, predominantly the Kupffer cells. Neither complement nor other plasma factors appear to play a significant role in the initial stage of the phagocytosis of endotoxin. This suggests that the early phase of this process consists of a direct interaction between endotoxin and specific endotoxin receptor or binding sites on the macrophage cell membrane.

57. Vascular responsiveness of the in situ perfused dog pancreas. R. J. Gorczynski, J. A. Spath, Jr., and A. M. Lefer. Europ. J. Pharmacol. 27: 68-77, 1974.

The in situ perfused dog pancreas was utilized to investigate: (a) the contribution of humoral vasoactive agents which are released in shock to maintain the development of pancreatic hypoperfusion, (b) the effectiveness of glucocorticoids as splanchnic vasodilator agents as a possible mechanism of their beneficial effect in shock, and (c) the pancreatic vascular response to the cardiac glycoside, ouabain. Close intra-arterial injection of norepinephrine, epinephrine, vasopressin and angiotensin in concentrations present in shock animals significantly increased pancreatic vascular resistance, whereas bradykinin, prostaglandins E_1 and E_2 exerted a vasodilator effect. The glucocorticoids, methylprednisolone and dexamethasone, were without net vascular effect in the perfused pancreas at concentrations comparable to those known to be protective in hemorrhagic shock. Ouabain produced a well maintained influence in pancreatic vascular resistance. It is concluded that the release of vasoactive agents may significantly influence the pancreatic vascular response to prolonged hemorrhage. Use of ouabain in the treatment of circulatory shock states could result in severe deleterious effects to the organism because of its prolonged vasoconstriction of the pancreatic vasculature. No evidence of a vasodilator action of glucocorticoids in the pancreatic vasculature was found, suggesting other mechanisms for the protective action of these agents in shock.

58. Comparison of leukocytic pyrogen and leukocytic endogenous mediator. C. R. Merriman, L. A. Pulliam, and R. F. Kampschmidt. Proc. Soc. Exptl. Biol. Med. 154: 224-227, 1977.

Leukocytic pyrogen was subjected to a 5-step purification scheme, and quantitative assays for both leukocytic pyrogen and leukocytic endogenous mediator (LEM) were made. At each step of the purification scheme, the active fractions, in addition to producing fever, lowered plasma iron and zinc concentrations, elevated fibrinogen concentrations, and caused a release of neutrophils from bone marrow. It appears, therefore, that LEM and leukocytic pyrogen are the same molecule.

59. In vitro effect of ascorbic acid on corticosteroid-caused neutrophil dysfunction. G. E. Olson and H. C. Polk, Jr. J. Surg. Res. 22: 109-112, 1977.

The depression of the phagocytic and/or bactericidal capacity of neutrophils (PMN) by various corticosteroids has been well documented. Therapeutic titers of some corticosteroids may lead to an impaired inflammatory response and may result in an increased susceptibility to infective processes, even with an adequate number of phagocytic cells. The present investigation was designed to evaluate in vitro the phagocytic-bactericidal capacity of corticosteroid-ascorbic acid-modified PMN with a more sensitive method.

The phagocytic-bactericidal capacity of human polymorphonuclear leukocytes (PMN) for Staphylcoccus aureus 502A was significantly depressed by a so-called pharmacologic dose of hydrocortisone sodium phosphate (0.08 mg/ml) in the medium. This effect was partially neutralized by the administration of a therapeutic dose of ascorbic acid (0.167 mg/ml) in the medium, suggesting that the propensity of some glucocorticoids to enhance infection may be favorably influenced by ascorbic acid.

60. The effect of hydrocortisone acetate and azathioprine (Imuran) on the kinetics of neutrophilic polymorphonuclear leucocytes during an acute inflammation. J. Thompson, A. E. Gassmann, and R. Van Furth. Proc. Soc. Exptl. Biol. Med. 154: 17-21, 1977.

The course of the number of neutrophilic polymorphonuclear leukocytes during an acute inflammation in the peritoneal cavity was studied in mice treated with hydrocortisone or azathioprine. The results show that in these animals the number of neutrophilic granulocytes appearing in the inflammatory exudate is similar to that in animals not treated with these antiinflammatory drugs. This study indicates that glucocorticosteroids do not affect the vascular permeability for granulocytes or the motility of these cells, and that during azathioprine treatment the bone marrow contains a sufficient number of neutrophils that can be released into the circulation.

61. Effect of flow rate and glucose concentration on glucose uptake rate by the rat limb. B. Grubb and J. F. Snarr. Proc. Soc. Exptl. Biol. Med. 154: 33-36, 1977.

In vivo a number of factors can influence the rate of glucose uptake by skeletal muscle. The permeability of muscle to glucose and the effect of insulin have undoubtedly received the most attention. No studies could be located in which the effect of flow rate on the glucose uptake rate by skeletal muscle was studied, although this parameter has been investigated in the brain. The purpose of the present investigation is to determine the influence of glucose concentration and flow rate on the rate of glucose uptake by the perfused rat hindlimb (basically a muscle preparation).

This investigation has defined a relationship that glucose concentration and flow rate have upon the rate of glucose uptake by the resting perfused rat hindlimb. The glucose uptake rate is linearly related to the perfusate glucose concentration within the range of glucose concentration studied (50-400 mg%). It has also been determined that glucose uptake rate is hyperbolically related to the perfusate flow rate. It appears as though the glucose uptake rate is flow limited for rat skeletal muscle at rest.

62. Left ventricular compliance and pulmonary artery end-diastolic pressure. W. H. Herbert. N. Y. St. J. Med. 77: 344-348, 1977.

There is yet no unanimity as to the efficacy of the use of the pulmonary artery end-diastolic pressure and wedge pressure as an accurate reflection of left ventricular end-diastolic pressure. Since the reports with poor correlations included patients with left ventricular disease, a further assessment of pulmonary artery-left ventricular dynamics in such patients was made. This study demonstrated that many of these patients manifested a reverse pressure gradient across the pulmonary vascular bed; that is, at end-diastole, left ventricular end-diastolic pressure was higher than pulmonary artery end-diastolic pressure. This reverse gradient was related significantly to left ventricular end-diastolic pressure ($p < 0.001$). These findings were correlated to the established reduction in left ventricular compliance observed in patients with coronary artery disease and/or myocardial infarction. Since many patients requiring left ventricular filling pressure assessment are being monitored specifically for these problems, it is important to appreciate the frequent failure of the pulmonary artery end-diastolic pressure to reflect the left ventricle in this group.

A substantial elevation in LVEDP due to reduced compliance may be found in many patients with coronary artery disease. However, it is apparent that the measurements of PAEDP in these patients may be entirely normal, and if utilized as a direct reflection of LVEDP such readings may give the erroneous impression of a normal left ventricular filling pressure. Although PAEDP changes may accurately reflect the direction of change of LVEDP, such data will frequently prove insufficient for patient management.

63. A reexamination of the influence of muscle length on myocardial performance. B. R. Jewell. Circ. Res. 40: 221-230, 1977.

Conclusions:

1. Length-dependence of activation accounts almost entirely for the dependence of tension production on muscle length over the ascending limb of the length-tension relation in isolated papillary muscles.

2. If the inotropic state of the muscle is equated with the degree of activation of the contractile system, then muscle length influences inotropic state and a change of muscle length must therefore be regarded as an inotropic intervention.

3. If these results are applicable to the intact heart, then diastolic volume and inotropic state cannot be regarded as independent regulators of cardiac output.

Muscle length and contractility or the inotropic state of the muscle have been regarded as amenable to independent manipulation as experimental variables, and the quest for the perfect index of contractility has rested squarely on the belief that some fortunate person would, one day, find a measure of mechanical performance that could be shown to depend on the inotropic state of the muscle and to be independent of muscle length. The conclusion reached in this article is that (in the isolated papillary muscle at least) there can be no such index of contractility because the inotropic state of the muscle is strongly influenced by its length.

64. Subcellular reactions to injury. I. Ultrastructural and biochemical investigations on the hepatic cellular damage produced by haemorrhagic shock in dogs. M. A. Russo, A. Conforti, A. Bellavia, and F. Grassetti. J. Path. 121: 107-113, 1977.

The purpose of the present study of cellular reactions to injury was to attempt to correlate the simultaneous morphological and biochemical-biophysical alterations, in order to shed light on the pathogenetic relationship between the two series of data and to suggest a unitary interpretation.

An experimentally induced haemorrhagic shock in dogs may produce cellular damage by three main mechanisms: anoxia, haemodynamic alterations and metabolic deprivation. While the last two factors play an important role in sudden, acute and chronic conditions respectively, the first seems to be the fundamental factor involved in the 1st 2 hr of bleeding. Since an anoxic cell injury is not modified by either hyper or hypocapnia this factor has not been considered in the discussion. On the other hand, anoxic cell changes share a striking similarity with cellular damage produced by ischaemia; it must therefore be stressed that in all these various conditions the basic functional alteration is the decreased oxygen consumption.

The ultrastructural changes produced by haemorrhagic shock in hepatocytes have been studied in dogs. The associated biochemical and biophysical systemic alterations allow us to propose a unitary pathogenetic mechanism of the cellular injury based on oxygen deprivation and its effect on the function and structure of the cellular compartments.

65. Treatment of shock in myocardial infarction. S. A. Johnson and R. M. Gunnar. J. Am. Med. Assoc. 237: 2106-2108, 1977.

Once cardiogenic shock has been diagnosed, one should insert an arterial line, a Swan-Ganz catheter to the pulmonary artery position where wedge pressures can be recorded, and a Foley catheter. Treatment is then determined on the basis of the hemodynamic measurements.

1) If the arterial pressure is low and the wedge or pulmonary-artery diastolic pressure is also low, then expand volume with dextran 40, albumin, or saline (100 ml/15 min) until wedge pressure reaches 18 mmHg.

2) If arterial pressure is low but wedge pressure is 18 mmHg or above, then infuse levarterenol bitartrate, 4-8 mg in 500 ml, to maintain intraarterial pressure at 100 to 110 mmHg systolic; or dopamine, 200 mg in 250 ml or 5% dextrose in water at rates up to 0.5 mg/min. Dopamine is preferable to levarterenol if arterial pressure can be maintained with low dosage levels and without excessive tachycardia.

3) If arterial systolic pressure is above 110 mmHg and wedge pressure is elevated above 18 mmHg, then a slow infusion of sodium nitroprusside beginning at 0.5 mg/ml/min may be administered cautiously.

4) If arterial pressure is maintained with levarterenol or dopamine but wedge pressure remains elevated, digitalize slowly with 0.125 mg i.v. every 4 hr to a total dose of 0.5 to 1.0 mg.

5) If the patient's condition does not stabilize rapidly or requires increasing amounts of pressor medications to maintain arterial pressure, and if the wedge pressure is elevated, intraaortic balloon counterpulsation should be initiated.

66. Gram-negative rod bacteremia: microbiologic, immunologic, and therapeutic considerations. UCLA Conference; Moderator: L. S. Young; Discussants: W. J. Martin, R. D. Meyer, R. J. Weinstein, and E. T. Anderson. Ann. Int. Med. 86: 456-471, 1977.

During the last two decades, gram-negative rod bacteremia has become the leading infectious disease problem in American hospitals. With improvements in conventional microbiologic techniques, bacteremic infection can be diagnosed reliably within 3 days using only three sets of cultures. Clinical management still requires aggressive, presumptive use of antimicrobials in patients with the most adverse host factors. In the latter group, the use of combinations of antibiotics that interact synergistically in vitro has improved clinical results. In bacteremia due to anaerobes, particularly Bacteroides species, drainage of infected sites is probably more important than specific drug therapy. Various host defects have been associated with gram-negative bacteremia; the most common in the nonleukopenic patient is impaired opsonization. The evidence that endotoxins are involved in the pathophysiology of gram-negative bacillemia is inferential. Nevertheless, both clinical and experimental evidence suggest that active or passive immunization with endotoxin components or antigens similar to gram-negative polysaccharides may be protective.

67. Disseminated intravascular coagulation and refractory shock induced by splanchnic metabolic acidosis. N. Nagasue, A. Iwaki, H. Yukaya, N. Koyanagi, M. Kobayashi, and K. Inokuchi. Surg. Gynec. Obstet. 144: 519-524, 1977.

In 8 dogs, acidosis was induced by the infusion of lactic acid into the superior mesenteric artery in a dose of 5.0 to 12.5 millimoles per kg during a 30-min period. Four dogs out of five in which the lowest pH of arterial blood was lower than 7 developed a typical acute disseminated intravascular coagulation, accompanied by a sudden elevation of arterial and portal venous pressure. In these four dogs, refractory shock developed between 0.5 and 5 hrs after lactic acid infusion. The other four without disseminated intravascular coagulation maintained a normal blood pressure and survived until sacrifice 6 hr after infusion. In two dogs, systemic infusion of 10 millimoles per kg was performed in the same interval as the former. Both died from cardiac failure without occurrence of disseminated intravascular coagulation before the infusion was completed. The dogs with disseminated intravascular coagulation revealed a marked deterioration of coagulative system and generalized thrombi in the intestine, liver, lung and kidney. Minimal changes in these parameters were observed in the dogs without disseminated intravascular coagulation. The results suggest that the infusion of lactic acid into the superior mesenteric artery is a convenient model for the production of disseminated intravascular coagulation and resultant shock.

68. Prostaglandin-like substances in coronary venous blood following myocardial ischemia. R. J. Kraemer, T. M. Phernetton, and J. D. Folts. J. Pharm. Expt. Ther. 199: 611-619, 1976.

Twelve anesthetized open chest dogs received an intracoronary infusion of 20 μCi of ^{3}H-arachidonic acid through the left anterior descending coronary artery. A control blood sample was then taken from the great cardiac vein. The left anterior descending coronary artery was occluded for 10 minutes and then released. A second cardiac vein blood sample was obtained during the coronary reactive hyperemic response. The pre- and postocclusion blood samples were analyzed for prostaglandin (PG)-like substances using thin-layer chromatography and analysis for radioactivity. There was an increase in PGE_2- and PGA_2-like substances,

and arachidonic acid found in the postocclusion samples. PGE_2 appears to be the predominant prostaglandin formed. Three animals received 10 mg/kg of indomethacin i.v. 1 hr before the ^3H-arachidonic acid infusion. Pretreatment with indomethacin abolished the release of PGE_2 and PGA_2-like substances but not arachidonic acid and reduced the reactive hyperemic response in magnitude and duration. Reactive hyperemia after a 10-minute occlusion was studied in 5 dogs before and 1 hr after the intravenous administration of 10 mg/kg of indomethacin. The control coronary flow and peak reactive hyperemic response were significantly reduced by the indomethacin. These studies suggest that myocardial ischemia promotes the synthesis and release of PG-like substances which may play a role in reactive hyperemia.

69. Intestinal lysosomal enzyme activity in regional simulated shock: Influence of methylprednisolone and albumin. U. Haglund, K. Lundholm, O. Lundgren, and T. Schersten. Circ. Shock 4: 27-34, 1977.

A 2-hr period of regional intestinal simulated shock in cats results in small intestinal mucosal lesions and a general cardiovascular derangement, probably secondary to the release of cardiotoxic material into the intestinal venous blood. These phenomenona are accompanied by release of lysosomal and cytoplasmic enzymes from the intestinal tissue. The effects of methylprednisolone treatment and deposition of albumin in the intestinal lumen during the regional shock period were studied. Administration of methylprednisolone early and late in the regional shock period prevented mucosal lesions and cardiovascular deterioration as well as lysosomal and cytoplasmatic enzyme release. Albumin deposition in the intestinal lumen during the regional shock period prevented lysosomal enzyme release and cardiovascular derangement and to a minor extent mucosal lesions. It is suggested that release of intestinal lysosomal enzymes is of importance for development of mucosal lesions and for production of cardiotoxic material.

70. Cerebral hemodynamics, vascular reactivity, and metabolism during canine endotoxin shock. J. L. Parker and T. E. Emerson, Jr. Circ. Shock 4: 41-53, 1977.

Cerebral hemodynamics, vascular reactivity, and metabolic alterations were studied in anesthetized, spontaneously respiring dogs for 4-6 hr of gram-negative endotoxin shock. Cerebral venous outflow (cerebral blood flow) was measured directly from the cannulated confluence of the sagittal, straight, and lateral sinuses, with the lateral sinuses occluded. Cerebral blood flow and cerebral perfusion pressure decreased immediately upon administration of 1, 2 or 5 mg/kg endotoxin and consistently remained below control values. By the 4th hr of shock, cerebral blood flow was decreased 37, 48, and 45% respectively. Cerebral vascular resistance initially decreased, then progressively increased to levels significantly above control, and it was primarily responsible for the reduced cerebral blood flow in the later stages of shock. Cerebral autoregulatory and "venous-arteriolar" responses were well maintained, although cerebral vascular reactivity to arterial hypercapnia was depressed. Cerebral venous blood pH and pO_2 decreased, and arterial-venous differences of percentage oxygen saturation, total CO_2, and HCO_3^- increased. These alterations in cerebral vascular hemodynamics and tissue acid-base balance indicate that cerebral ischemia and resulting acidosis occur during canine endotoxin shock.

71. Comparative splanchnic blood flow effects of various vasodilator compounds. N. W. Robie and J. L. McNay. Circ. Shock 4: 69-78, 1977.

Visceral blood flow distribution was examined during infusion of three vasodilators at doses that produced similar depression of systemic arterial pressure. The studies were performed in pentobarbital-anesthetized dogs using the radioactive microsphere technique. Minoxidil did not alter renal, total visceral, or visceral organ flow distribution with the exception of a modest increase in relative stomach blood flow. Nitroprusside increased the percentage of total visceral flow to the spleen and the hepatic artery. Dopamine increased blood flow to the stomach, intestine, and kidney. After phenoxybenzamine, the augmentation of stomach blood flow by dopamine was greatly increased, while blood flow to the splenic, pancreatic, and hepatic arteriolar vascular beds decreased. The decreases in blood flows may be due to decreased perfusion pressure in the absence of active vasodilation or to myogenic or metabolic autoregulation. Thus, at equivalent hypotensive responses, the vasodilator compounds that were studied produced markedly different patterns of visceral blood flow.

72. The chemical nature of a pancreatic cardiodepressant factor. R. D. Goldfarb and P. Weber. Circ. Shock 4: 95-100, 1977.

The presence of a cardiodepressant factor of pancreatic origin has been reported in the plasma of experimental animals and man in a variety of shock states. It has been suggested that the depression of developed tension of the isolated cat papillary muscle may be caused by excess NaCl in the bathing medium rather than a specific cardiodepressant peptide. Incubated pancreatic homogenate was used as a source of this factor, and after protein precipitation, ultrafiltration (10,000 and 1,000 WM), dialysis and lyophilization, the residue was applied to a Sephadex G-10 column in order to ensure the removal of all salts. The protein effluent of the Sephadex column contained all the cardiodepressant activity of the filtered, dialyzed pancreatic homogenate and none of the salt content. To further isolate this cardiodepressant factor, the active residue was applied to a cellulose column and eluted with butanol: glacial acetic acid: water (25:26 v/v/v). This elution gave 8 distinct peptide peaks, one of which, peak 4, contained significant depressant activity. Thus, a cardiodepressant peptide of approximately 250-1,000 MW exists in pancreatic homogenates and this compound is not excess NaCl in the assay system.

73. Effects of ganglionic blockade upon the renal and cardiovascular dysfunction induced by thermal injury. R. Turner, H. F. Carvajal, and D. L. Traber. Circ. Shock 4: 103-113, 1977.

Studies to test the effects of partial ganglionic blockade on renal and cardiovascular function were carried out in 16 mongrel dogs that under chloralose anesthesia had been subjected to full thickness flame burns to approximately 25% of their body surface. All animals received intravenous fluid replacement according to the same resuscitation formula used in burned children. Half of the animals received 0.3 mg/kg of chlorisondamine hydrochloride 40 min after the burn; the remaining 8 dogs received only the vehicle. Among the variables monitored before burning and before and after blockade were glomerular filtration rate, renal plasma flow, water and osmolar clearance, sodium and potassium excretion, cardiac output, mean arterial, right atrial,

and left ventricular end diastolic pressure, peripheral resistance, peak dP/dt/P, blood pH, and blood gases. Analysis of the data has revealed that pharmacologic blockade of the sympathetic system during the immediate post-burn period results in a marked improvement in cardiac output and moderate improvement in kidney function.

74. Skeletal muscle pH, O_2, CO_2, and electrolyte balance during hemorrhagic shock. R. F. Bond, E. S. Manning, and L. C. Peissner. Circ. Shock 4: 115-131, 1977.

Previous reports have indicated a significant degree of hindlimb skeletal muscle vasodilation coincident with the decompensatory phase of shock induced by prolonged hemorrhagic hypotension. The first objective of the present investigation was to examine the relationship between this apparent vascular decompensation and the arterial and venous skeletal muscle PO_2, PCO_2, $\dot{V}O_2$, $\dot{V}CO_2$, pH, Na^+, and K^+. The second objective was to examine the possibility that a stable blood-borne, remotely or locally released, vasodilator substance caused the vascular decompensation. Anesthetized dogs were bled in 5 ml/kg steps into a suspended reservoir until mean arterial pressure (MAP) was 35-40 mmHg; this pressure was maintained until signs of decompensation were apparent. The blood remaining in the reservoir was returned and the animals were followed until MPA fell below 50 mmHg. MAP, central venous pressure (CVP), lead II of ECG, heart rate (HR), and skeletal muscle venous flow were monitored and correlated with arterial and venous CO_2, O_2, and electrolytes. The results suggest that the skeletal muscle vascular decompensation was not caused by a stable blood-borne substance but may at least in part be due to the increased H^+ and K^+ in skeletal muscle blood and to mild skeletal muscle hypoxia.

75. Histamine biosynthesis in shock. M. J. Galvin, Jr., O. R. Bunce, and S. M. Reichard. Circ. Shock 4: 133-141, 1977.

The histidine decarboxylase activity of the lung and spleen was determined in rats made resistant to trauma either by prior sublethal exposure or by injection of extracts prepared from the spleens and plasma of trauma-resistant rats. The data describe the posttraumatic period in the normal animal as being associated with an increased histidine decarboxylase activity. In trauma-resistant animals, changes in the enzyme activity were prevented in the lung and were less pronounced in the spleen. The administration of extracts from trauma-resistant rats was similarly effective in impeding the changes in enzyme induction following trauma. It is suggested that an active humoral factor previously shown to be elaborated during conditioning and associated with the RES may act by inhibiting the activation of histidine decarboxylase.

76. The influence of venous return on cardiac mechanical and sarcoplasmic reticulum function during endotoxemia. M. L. Hess, M. E. Soulsby, J. A. Davis, and F. N. Briggs. Circ. Shock 4: 143-152, 1977.

E. coli endotoxin (0.03 mg/ml) added to blood perfusing a heart-lung preparation with a venous return of 600 ml/min produced a significant depression in ventricular function within 4 hours. Fragmented sarcoplasmic reticulum isolated from the myocardium of the endotoxin-perfused heart-lung preparations showed depressed calcium uptake rates and ATPase activity. When venous return was increased to 1,200 ml/min, gram-negative endotoxin had no effect on ventricular function, isolated fragmented sarcoplasmic reticulum calcium

uptake, or ATPase activity. These observations suggest that gram-negative endotoxin or a product thereof acts in synergism with low venous return in order to depress myocardial function.

77. Humoral factors in shock causing bradycardia and myocardial depression. D. David, H. Hilewitz, and S. Rogel. Circ. Shock 4: 153-161, 1977.

Hypovolemic shock was maintained for 6 hours in dogs in which the heart was hemodynamically protected by a biological model described earlier. Blood of these dogs was exchanged with that of healthy dogs in which myocardial tension and heart rate were continuously monitored. It was found that rate and force decline in the recipient dog in a fashion similar to the drop in the animal in shock. If, however, the pH of the infused blood was raised to normal, the bradycardia in the recipient dog was prevented but the myocardial depression was not abolished. Administration of aprotinin alone did not prevent the bradycardia or depression of contractility, whereas correction of the pH and treatment with aprotinin not only prevented the decline in both but led also to a transient increase in myocardial tension of the recipient animal. The results seem to indicate that 1) in shock myocardial depression and cardiac slowing are induced by humoral factors transferable by blood to a normal animal, 2) acidity causes the bradycardia but not drop of tension, 3) aprotinin prevents the depression of contractility only in a normal pH medium, and 4) aprotinin may prevent the action of a preformed myocardial depressant factor rather than inhibit its formation.

78. The effects of reserpine on myocardial lesions in dogs subjected to hemorrhagic shock. T. C. Graham, D. B. Hackel, A. Wechsler, and W. Hardaker. Circ. Shock 4: 163-169, 1977.

Anesthetized dogs were subjected to severe hemorrhagic hypotension, with blood pressure maintained at 35 mmHg for 30-90 min. In these dogs myocardial zonal lesions were present and subendocardial hemorrhage and necrosis resulted. In two other groups of dogs, similarly subjected to hemorrhage but previously depleted of catecholamines by a 3-day regime of reserpine treatment, there was a markedly lower or no incidence of myocardial lesions.

79. Effects of dopamine on endotoxin and hemorrhagic shock in the canine stomach. Y.-J. Kuo, A. C. Chou, T. M. W. Ma, and L. L. Shanbour. Circ. Shock 4: 171-180, 1977.

Studies were conducted to evaluate the effects of dopamine on gastric electrophysiology in endotoxin and hemorrhagic shock. Intraarterial infusion of dopamine (15.5 or 31 μg/kg/min) in the in vivo stomach preparation produced an immediate decrease in electrical potential difference (PD), which then returned and exceeded control values. No changes in resistance (R) and blood pressure were observed. These electrophysiological responses of the gastric mucosa to dopamine are very similar to the actions of epinephrine. The in vitro studies demonstrated that active transport of Na^+ was stimulated with an addition of dopamine or epinephrine (2×10^{-4}M) to the serosal solutions of the isolated gastric mucosa. In additon, the in vivo studies demonstrated that both 40% hemorrhage and 1 mg/kg of endotoxin given as an i.v. bolus decreased PD and blood pressure and increased R although dopamine was continuously infused intraarterially for 60 min prior to the following hemorrhage or endotoxin. Administration of endotoxin at the onset of dopamine infusion decreased both blood pressure and PD initially. While PD showed a complete recovery at a later stage, blood pressure never returned to control

levels. These results, combined with previous observations, suggest that: 1) dopamine has no beneficial action on the gastric mucosa during hemorrhagic or endotoxin shock; 2) dopamine acts on the electrophysiology in vivo and Na^+ fluxes in vitro in the gastric mucosa in a manner similar to epinephrine; and 3) decrease in blood flow may be responsible for the observed decrease in transmural PD after dopamine and epinephrine in vivo.

80. In vitro effects of E. coli endotoxin on fatty acid and lactate oxidation in canine myocardium. M.-S. Liu and J. J. Spitzer. Circ. Shock 4: 181-190, 1977.

The purpose of this study was to study the in vitro effect of E. coli endotoxin on the oxidation of palmitate, palmitoyl CoA, and lactate by canine heart homogenate. Heart homogenates were incubated in calcium-free Krebs-Ringer-phosphate buffer in the presence of a ^{14}C-labeled substrate. Oxidation of the individual substrate was calculated from the rate of $^{14}CO_2$ production. The rate of oxidation of palmitate, palmitoyl CoA, and lactate was proportionally inhibited by increasing amounts (80-800 μg) of endotoxin. The decrease in substrate oxidation could be mimicked by adding calcium chloride to the tissue preparation, and could be effectively prevented by the chelating agent, EDTA. Ionic calcium was released from tissue stores during incubation of the tissue preparation with endotoxin. These findings demonstrate that E. coli endotoxin inhibits substrate oxidation by heart homogenates when incubated under in vitro conditions. The data also suggest that the inhibition may be mediated by ionic calcium released from the tissue in response to the action of endotoxin.

81. Myocardial fatty acid and lactate metabolism after E. coli endotoxin administration. M.-S. Liu and J. J. Spitzer. Circ. Shock 4: 191-200, 1977.

The effect of E. coli endotoxin administered in vivo was studied on the oxidation and esterification of fatty acids as well as the oxidation of lactate by canine heart homogenate. Dogs were anesthetized 10 minutes or 2, 4, or 10 hours following the intravenous administration of E. coli endotoxin. Myocardial homogenates were then prepared and the metabolism of free fatty acid or lactate was investigated under in vitro conditions. Oxidation of palmitate by homogenates of endotoxin injected dogs remained relatively constant but lactate oxidation was enhanced by 34.6%, 40.2%, and 24.5%, 10 minutes, 4 hours, and 10 hours after endotoxin injection, respectively. Incorporation of palmitate into phospholipid and triglyceride was decreased by about one-third 10 minutes after endotoxin. Myocardial concentration of α-glycerophosphate and *l*-carnitine was increased by 56.8% and 35.6%, respectively, in the early phase, followed by a 78.8% increase in myocardial triglyceride content 10 hours after endotoxin administration. These findings demonstrate that after endotoxin injection, utilization of substrates by the myocardium was shifted in favor of lactate from palmitate. The depressed fatty acid incorporation into tissue lipids may also represent one of the early derangements in the pathogenesis of heart dysfunction in endotoxic shock.

82. Platelets, fibrinogen, and pulmonary haemodynamics in early experimental septic shock. H. E. Myrvold and D. H. Lewis. Circ. Shock 4: 201-209, 1977.

The relationships between platelet trapping, fibrinogen, and pulmonary haemodynamics after iv injection of disintegrated Pseudomonas bacteria into dogs were studied. Platelets were labeled with ^{51}Cr and fibrinogen with ^{125}I. The number of circulating platelets and white cells decreased abruptly within 2 min after injection, remained low at 5 min, and thereafter slowly increased. At the same time there was a transient increase of ^{51}Cr activity in the lung occurring simultaneously with a decrease in cardiac output and an increase in pulmonary vascular resistance. Pulmonary artery pressure remained constant during the first phase of the experiment and thereafter decreased. There were no signs of ^{125}I-fibrinogen accumulation in the lungs during the 2 hrs of the experiment. The results indicate that trapping of platelets and eventually leucocytes in the lungs are closely related to the initial pulmonary haemodynamic changes after injection of disintegrated bacteria, possibly both by release of vasoactive substances and mechanical blocking. This microembolism in the pulmonary microcirculation might be of importance for the development of the shock lung syndrome.

83. Leukocytosis and artifactual hypoglycemia. T. J. Goodenow and W. B. Malarkey. J.A.M.A. 237: 1961-62, 1977.

Two patients are described with asymptomatic low blood glucose and excessive in vitro consumption of glucose by leukocytes before separation of the serum for assay. This may be a more common problem than is appreciated and need not be associated with leukemia or extreme leukocytosis. The circumstances that allow this avoidable type of artifactural hypoglycemia may also produce factitious euglycemia during evaluation of suspected diabetes mellitus.

84. Myocardial depression during sepsis. R. D. Weisel, L. Vito, R. C. Dennis, C. R. Valeri, and H. B. Hechtman. Am. J. Surg. 133: 512-521, 1977.

Septic patients have an inordinately high incidence of cardiac, renal, and hepatic decompensation. The objectives of this study were to identify the causes of diminished cardiac reserves and of myocardial depression in sepsis and to develop guidelines for therapy.

Nearly half of both patient groups developed decreases in CI and LVSWI as the PAWP continued to increase. The downslopes occurred at relatively low PAWP and are taken as evidence of an abnormality of myocardial function in both survivors and nonsurvivors. The lower upslope of the performance curves in nonsurvivors indicates myocardial depression or a negative inotropic effect. To improve the prognosis of septic patients, careful attention should be paid to cardiac function.

85. An improved in vitro pyrogen test: To detect picograms of endotoxin contamination in intravenous fluids using Limulus amoebocyte lysate. R. Nandan and D. R. Brown. J. Lab. Clin. Med. 89: 910-918, 1977.

A method for in vitro pyrogen testing using Limulus amoebocyte lysate (LAL) has been described. The method is based upon the measurement of endotoxin-precipitable protein and can be used to measure picogram quantities equivalent to E. coli endotoxin in unknown solutions. When increasing concentrations of E. coli endotoxin

are added to a constant amount of LAL and the reaction is allowed to proceed to completion, there is a proportional increase in the protein precipitated by endotoxin. Therefore, by measuring the amount of protein precipitated from LAL, it is possible to determine the equivalent E. coli endotoxin concentration in unknown solutions, when samples of the unknowns are run simultaneously with E. coli endotoxin standards and negative controls. The endotoxin proportional precipitation of protein occurs in reaction mixture showing gelation as well as in reaction mixture where the levels of endotoxin are lower than required for gelation. Determination of precipitated protein provides greater sensitivity for endotoxin detection than the gelation methods currently in use.

86. Myocardial ischemia. L. D. Hillis and E. Braunwald. New Engl. J. Med. 296: 971-978; 1031-1041; 1093-1096, 1977.

The purpose of this paper (written in three parts) is to review recent developments in three areas: the effects of ischemia on myocardial contractility; the recognition and quantification of ischemic damage; and the protection of the ischemic myocardium in an effort to reduce the quantity of tissue that ultimately becomes necrotic after coronary-artery occlusion.

87. Pitfalls of Swan-Ganz catheterization. B. Shin, R. J. Ayella, and T. C. McAslan. Crit. Care Med. 5: 125-127, 1977.

In 60 patients in whom Swan-Ganz catheters apparently had been positioned correctly, the balloon was visualized by inflation with radiopaque contrast medium. Sixteen were located peripherally; in 15 of these 16, the balloon inflated eccentrically and in each of these instances, an accurate wedge pressure could not be obtained. One patient in this group had an episode of hemoptysis immediately prior to detection of the peripheral location and eccentric inflation of the balloon.

The correct placement and safe use of the Swan-Ganz catheter demand that the catheter tip be located in a large pulmonary artery and that redundant loops of catheter be avoided to prevent subsequent peripheral migration. Identification of peripheral placement and eccentric inflation should be suspected if a pulmonary wedge pressure is obtained with a significantly smaller volume of air than the balloon capacity. The use of a continuous flush system will provide an additional alert by a steady rise in the pseudowedge pressure on attempted balloon inflation.

88. Tissue blood flow in brain, liver, renal cortex, and renal medulla in experimental hemorrhagic shock. H. Hirasawa, M. Odaka, Y. Tabata, H. Kobayashi, and H. Sato. Crit. Care Med. 5: 141-145, 1977.

Cerebral, hepatic, renal cortical, and medullary tissue blood flows of the dog during hemorrhagic shock were measured continuously using the thermoelectrical method. The effects of blood replacement, adrenergic α-stimulator and -blockade and hydrocortisone on the tissue blood flows were studied.

After hemorrhage, cerebral blood flow was well maintained while renal cortical blood flow was poorly maintained. Following retransfusion, the blood flow returned rapidly to the brain and slowly to the renal cortex. Norepinephrine, phentolamine, and hydrocortisone were not effective in maintaining the organ blood flows in shock. However, when morepinephrine was given systemically and phentolamine administered to the renal artery simultaneously during shock, both cerebral and renal flows were well maintained. After the blood replacement and administration of α-blockade or hydrocortisone, all the measured blood flows returned to normal levels.

89. Mediation of hyperthermia by prostaglandin E_2: A new hypothesis. J. A. Splawinski. Naunyn-Schmiedeberg's Arch. Pharmacol. 297: S95-S97, 1977.

In rat hypothalamus prostaglandin (PG) E_2, unlike $PGF_{2\alpha}$ or arachidonic acid, shared the site of hyperthermic action with E. coli endotoxin. The in vitro catabolism of PGE_2 in the hypothalami of endotoxin-treated rats was significantly suppressed. It is proposed that endotoxin fever in rats is due to the inhibition of PGE breakdown in the hypothalamus.

90. Aspects of prostaglandin function in the lung. A. A. Mathe, P. Hedqvist, K. Strandberg, and C. A. Leslie. New Engl. J. Med. 296: 850-855; 910-914, 1977.

The purpose of this two-part report is to review the effects of one autacoid, the prostaglandins (PG's), on both respiratory and nonrespiratory functions of the lung. The following topics are discussed: effects of prostaglandins on lung vasculature and airways; prostaglandin synthesis and catabolism in lung; prostaglandin uptake and inactivation in lung; prostaglandin release from "healthy," antigen-sensitized and anaphylactic lung; inhibition of prostaglandin release; prostaglandins and other mediators of anaphylaxis, prostaglandins and the autonomic nervous system; prostalgandins in healthy and asthmatic man; and prostaglandins as therapeutic agents.

91. Septicemia in a community hospital 1970 through 1973. W. E. Scheckler. J.A.M.A. 237: 1938-1941, 1977.

Septicemia developed in 34 patients per 10,000 admissions to a community hospital during 1970 through 1973. Two thirds of the 207 patients had community-acquired septicemia, and one third had nosocomial septicemia. Septicemia-related mortality was 20.3%. Mortality and incidence of septicemia was substantially higher in patients with ultimately fatal and rapidly fatal underlying diseases. Septicemia was associated with shock in 9.7% of the patients. Foley catheterization and prophylactic antibiotic therapy could not be implicated as major risk factors for the development of septicemia. This study shows an incidence of gram-negative bacteremia, septic shock, and mortality substantially less than that described in published data from noncommunity hospitals.

92. Changes in hemostatic system after application of a tourniquet. L. Klenerman, R. Chakrabarti, I. Mackie, M. Brozovic, and Y. Stirling. Lancet 1: 970-972, 1977.

In 35 patients undergoing routine orthopedic operations in which occlusive tourniquets were used there was a pronounced rise in fibrinolytic activity in the systemic circulation which lasted for at least 15 minutes after the release of the tourniquet; this response was seen after operations on both arms and legs. In contrast there was no increase in fibrinolytic activity in the systemic circulation associated with venous occlusion. Neither the application of a tourniquet nor venous occlusion resulted in changes in factors V or VIII, fibrinogen, or platelet-count. The application of a completely occlusive tourniquet might be a simple form of prophylaxis against deep-vein thrombosis and would avoid the disadvantages of using heparin.

93. The effect of 6-hydroxydopamine-induced hepatic sympathectomy on the early hyperglycemic response to surgical trauma under anesthesia. W. W. Lautt and M. G. Cote. J. Trauma 17: 270-274, 1977.

A single intraportal injection of 6-OH-DA (50 mg/kg) in rats results in a functional hepatic sympathectomy 6 days following the injection. Laparotomy and mild abdominal exploration under pentobarbital anesthesia resulted in elevated plasma glucose levels within 15 minutes as a result of activation of the sympathetic nerves to the liver and adrenal gland discharge. The hyperglycemic response to trauma was reduced by fasting. The hyperglycemic response was examined in untreated rats, 6-OH-DA pretreated rats, bilaterally adrenalectomized rats, and a group which had received 6-OH-DA pretreatment as well as bilateral adrenalectomy. In nonfasted rats the presence of intact sympathetic nerves or intact adrenals was sufficient to produce the hyperglycemia. To prevent the response both nerves and adrenals must be deactivated. The hepatic nerves are primarily responsible for the early hyperglycemic response to trauma in fasted rats while in fed animals the adrenals and hepatic nerves play a more equal role.

94. Hepatic dysfunction following trauma: Experimental studies. I. J. Sarfeh and J. A. Balint. J. Surg. Res. 22: 370-375, 1977.

These studies suggest that post-traumatic hepatic dysfunction results from hepatic ischemia due to altered splanchnic hemodynamics in shock. The influence of the hepatic dysfunction on ultimate recovery from severe injury is not known at present. However, jaundice has been shown to be a common sequel of severe trauma. The authors have shown that progressive jaundice in a severly injured patient indicates a poor prognosis. It is to be hoped that a better understanding of the mechanisms underlying post-traumatic hepatic dysfunction will allow better management of this potentially serious complication.

95. Liver and skeletal muscle mitochondrial function following burn injury. J. R. Aprille, J. A. Hom, and J. Rulfs. J. Trauma 17: 279-288, 1977.

The possibility of altered mitochondrial function consequent to burn injury was investigated. Mitochondria isolated from liver or skeletal muscle of burn-injured rats (20% tbs) were compared at 3 days postburn to shams and normal controls. Mitochondrial yields were the same for all groups. ADP:O ratios were in the theoretical ranges expected and did not differ among burn, sham, and normal animals. Respiratory control ratios (RCR's) were decreased in liver mitochondria, averaging 71.7% of normal for burned animals compared to 95.8% for the sham group. The loss of respiratory control in liver mitochondria implies inefficient use of substrate chemical energy and could contribute to postburn hypermetabolism. The different response of muscle mitochondria as compared to liver suggests that alterations may be organ specific.

96. In vitro function of granulocytes isolated from blood of normal volunteers using continuous-flow centrifugation in the IBM-Aminco Celltrifuge and adhesion-filtration leukapheresus using nylon fiber. P. H. Wade, E. M. Skrabut, L. Vinciguerra, and C. R. Valeri. Transfusion 17: 136-140, 1977.

Granulocytes were harvested from each of five healthy male volunteers once by continuous flow centrifugation with the IBM-Aminco Celltriguge, and once by

adhesion filtration leukapheresis with nylon fiber. Granulocyte recovery and purity were significantly better with the filtration leukapheresis system than with continuous flow centrifugation. Measurements of trypan blue dye exclusion and muramidase activity were similar to those in control granulocytes regardless of the method of isolation. Granulocyte-stimulated oxygen consumption was diminished in granulocytes prepared by the adhesion filtration method, but normal in those prepared by continuous flow centrifugation with the IBM-Aminco Celltrifuge.

97. Comparison of endotoxin and leukocytic pyrogen pyrogenicity in newborn guinea pigs. C. M. Blatteis. J. Appl. Physiol. 42: 355-361, 1977.

Guinea pigs under 8 days of age generally are unable to develop fever in response to a standardized dose of endotoxin (2 μg/kg iv of Salmonella enteritidis [SE]). This study was undertaken to determine whether this lack of responsiveness might be due to an incapacity of leukocytes from young neonates to produce sufficient leukocytic pyrogen (LP). Three series of experiments were performed at T_a = 27°C: guinea pigs aged 0-2, 4, and 8 days were injected iv with: a) 2, 4, 8, or 16 μg/kg of SE, b) 0.1, 0.5, or 1.0 ml of LP generated by 8 μg of SE/25 X 10^6 leukocytes from adult guinea pigs (LP_a), or c) 0.1 or 1.0 ml of LP generated by 8 μg of SE/25 x 10^6 leukocytes from 0-5-, 6-12-, and 13-16-day-old guinea pigs (LP_n). Adult guinea pigs received iv 1.0 ml of LP_a or LP_n. The results revealed that fever could be induced in these animals from birth, but the required doses of SE, LP_a and LP_n were greater the younger the guinea pigs. Under these conditions, LP_n, regardless of the donors' ages, produced fever in all the recipients. It is concluded that the pyrogenic unresponsiveness of newborn guinea pigs to endotoxin may be related not to an inability of leukocytes from these neonates to elaborate LP, but rather to an insensitivity of, presumably, their hypothalmic febrogenic mechanisms to low levels of LP.

98. Modulation of phagocytosis by and lysosomal enzyme secretion from guinea-pig neutrophils: Effect of nonsteroid anti-inflammatory agents and prostaglandins. R. J. Smith. J. Pharmacol. Exper. Ther. 200: 647-657, 1977.

Guinea-pig neutrophils released lysosome granule-associated β-glucuronidase, but not cytoplasmic lactate dehydrogenase during cell contact with and phagocytosis of serum-treated zymosan particles. Narpoxen, chloroquine and indomethacin inhibited particle uptake by and lysosomal enzyme secretion from neutrophils incubated with zymosan in Krebs-Ringer phosphate medium, pH 7.4, at 37°C. Acetylsalicylic acid, fenoprofen and ibuprofen were inactive. Prostaglandins (PG) E_1, E_2, A_1, A_2, B_1 and B_2 reduced particle ingestion by and discharge of lysosomal enzymes from neutrophils. $PGF_{2\alpha}$ accelerated lysosomal enzyme release, had no effect on phagocytosis at high concentrations and inhibited both processes at low concentrations. $PGF_{1\alpha}$ was inactavie. In the presence of cytochalasin B, an agent which inhibits phagocytosis while having no effect on selective lysosomal enzyme secretion, naproxen, chloroquine and indomethacin, continued to inhibit the discharge of β-glucuronidase from neutrophils. PGE_1, PGE_2, PGA_1, PGA_2, PGB_1 and PGB_2 reduced lysosomal enzyme release from cytochalasin B-treated neutrophils. $PGF_{2\alpha}$ accelerated at high and inhibited at low concentrations the selective secretion of β-glucuronidase from cytochalasin B-treated neutrophils. $PGF_{1\alpha}$ was again inactive. These studies indicated that guinea-pig neutrophils are capable of a selective release of lysosomal enzymes (β-glucuronidase) during ingestion of serum-treated zymosan particles and that certain anti-inflammatory drugs and prostaglandins may function as modulators of the phagocytic release of lysosomal enzymes from neutrophils.

99. Disorders of leukocyte chemotaxis. R. Snyderman and M. C. Pike. Ped. Clin. N. A. 24: 377-393, 1977.

The rapid accumulation of inflammatory cells at sites of microbial invasion or neoplastic transformation is a central event in immunologically-mediated host defense. The availability of methodology to accurately quantify leukocyte migration in vitro has allowed the disclosure of previously unrecognized clinical disorders, namely leukocyte dysmotility syndromes. Although this area of clinical investigation is in its infancy, one can identify several processes associated with abnormal leukocyte accumulation. Abnormalities of immune recognition, chemotactic factor production, cellular motility or inhibitors of chemotaxis have been identified in different human diseases. In the upcoming years, pharmacological intervention directed at correcting specific causes of leukocyte dysmotility may well enhance our ability to treat certain infectious, inflammatory, and neoplastic diseases.

100. Redistribution of canine splanchnic blood flow following normotensive hemorrhage. G. L. Kauffman, Jr., and L. G. D'Alecy. J. Surg. Res. 22: 580-584, 1977.

Following normotensive hemorrhage, significant reduction in blood flow affected the gastric body mucosa (-62.3%), duodenum (-46.9%), and pancreas (-63.7%). Also following normotensive hemorrhage, no significant blood flow reduction occurred in the gastric antral mucosa, and mucosal blood flow reduction was significantly greater in the cardia than in the preantral region. Gastric antral blood flow is minimally sensitive to stress, suggesting a basis for the clinical observation of gastric body ulceration with antral sparing.

101. Transport and demand of oxygen in severe burns. M. G. S. Arturson. J. Trauma 17: 179-198, 1977.

Hypermetabolism, weight loss, and severe protein wasting characterize the metabolic response to thermal injury. The increased adrenergic activity following severe burns signifies a shift of flow of body substrate from storage to utilization and an increase in energy requirements. The critically injured patients have an accelerated glucose turnover and increased nitrogen loss; the main source of catabolized protein seems to be from skeletal muscle. The metabolic wheel has a tremendous speed.

102. Early prostaglandin release from the ischemic myocardium in the dog. M. L. Ogletree, J. T. Flynn, M. Feola, and A. M. Lefer. Surg. Gynec. Obstet. 144: 734-740, 1977.

Cellular consequences of myocardial ischemia were studied in anesthetized dogs. Confirmation of myocardial ischemia was provided by electrocardiographic and biochemical indexes. Prostaglandin $F_{2\alpha}$ release into coronary venous blood was significantly elevated during myocardial ischemia, whereas indomethacin treatment prevented this increase in coronary venous prostaglandin $F_{2\alpha}$ concentrations. No significant increase in prostaglandin E_2 release was observed in response to myocardial ischemia, but indomethacin treatment significantly reduced coronary venous prostaglandin E_2 concentrations below those of control values. Within one hour after occlusion of the coronary artery, the S-T segment was significantly altered, and coronary venous prostaglandin $F_{2\alpha}$ had increased significantly above the control concentration. These changes persisted during 4 hours of myocardial ischemia. Plasma creatine phosphokinase activity increased significantly after 2 hours of myocardial ischemia and remained elevated for the subsequent 2 hours of ischemia.

After 4 hours of myocardial ischemia, myocardial creatine phosphokinase activity of ischemic myocardium was significantly reduced, and labilization of myocardial lysosomes occurred in ischemic tissue. Indomethacin treatment prevented increases in prostaglandin release but did not influence other biochemical changes or the electrocardiographic response to ischemia. Thus, prostaglandin release by ischemic myocardial tissue is an early response to the ischemic stimulus.

103. Beneficial effects of arachidonic acid during hemorrhagic shock in the dog. J. T. Flynn and A. M. Lefer. Circ. Res. 40: 422-428, 1977.

Arachidonic acid (AA), precursor of the bisenoic prostaglandins was infused at a rate of 120 µg/kg/min into the vena cava of dogs subjected to hemorrhagic shock to assess the effects of stimulation of the prostaglandin (PG) synthetase system on the shock state. Hemorrhagic shock was induced by bleeding to a mean arterial blood pressure (MABP) of 40 mmHg for 150 min followed by reinfusion of all remaining shed blood. In sham shock dogs receiving AA vehicle (0.1 M Na_2CO_3), there were no significant changes in MABP, superior mesenteric artery flow (SMAF), renal artery flow (RAF), PGE_2 or $PGF_{2\alpha}$ concentrations, or in cathepsin D or myocardial depressant factor (MDF) activities during a 260-min experimental period. During oligemia, untreated hemorrhagic shock dogs exhibited dramatic reductions in MABP, SMAF, and RAF which were transiently restored following reinfusion, but markedly decreased 100 min after reinfusion. Cathepsin D, MDF, PGE_2, and $PGF_{2\alpha}$ values increased significantly in these dogs. AA given during oligemia did not prevent changes in SMAF or RAF, but maintained MABP at near-normal values after reinfusion. AA also significantly protected against the plasma accumulation of both cathepsin D and MDF in hemorrhagic shock dogs. Circulating $PGF_{2\alpha}$ and PGE_2 values increased rapidly in AA-treated dogs and plateaued at 3.6 and 4.8 times control values, respectively, during oligemia. Hemorrhagic shock dogs receiving AA plus Na meclofenamate, a PG synthetase inhibitor, were not significantly different from shock dogs receiving vehicle except that the circulating PG concentrations did not increase. Thus, products of the PG synthetase system appear to prevent the plasma accumulation of lysosomal hydrolases and of MDF, and may significantly preserve MABP after hemorrhagic shock in the dog.

104. Early changes in regional and global left ventricular function induced by graded reductions in regional coronary perfusion. D. D. Waters, P. Da Luz, H. L. Wyatt, H. J. C. Swan, and J. S. Forrester. Am. J. Cardiol. 39: 537-543, 1977.

To determine the sequence of changes in segmental myocardial function, regional lactate metabolism and global left ventricular function induced by mild regional ischemia, blood flow in the left anterior descending coronary artery of 10 dogs was reduced by 10% decrements with use of a screw clamp. At each level of flow, segmental mechanical function and regional metabolism were assessed, the former with use of a mercury-in-Silastic length gauge and the latter with transmyocardial lactate balance measurements obtained with sampling from the anterior interventricular vein. Coronary arterial flow at the onset of regional lactate production was 48±4% (mean ± standard error of the mean) of the control values. The onset of segmental mechanical dysfunction coincided with the onset of lactate production. Epicardial S-T segment abnormalities over the ischemic zone usually could not be detected until coronary flow was further reduced. After the onset of regional ischemia there was a linear correlation between coronary arterial flow and regional lactate production.

At the onset of mild regional ischemia, defined as the onset of regional lactate production, no significant or directionally consistent changes were noted in standard measurements of global left ventricular performance, including heart rate, mean aortic pressure, left ventricular end-diastolic pressure, cardiac output, stroke volume, stroke work and peak positive dP/dt (maximal rate of rise of pressure). However, peak negative dP/dt (maximal rate of pressure decrease) decreased from 99±2 to 89±3 % of the control value ($p<0.0005$) coincident with the onset of ischemia. It is hypothesized that dyssynchronous wall motion in the ischemic zone during isometric relaxation accounts for this decrease in peak negative dP/dt.

105. Shock lung with massive tracheal loss of plasma. L. B. Pemberton. J.A.M.A. 237: 2511-2513, 1977.

Fulminant pulmonary edema developed in two young, healthy adults within one hour after blood loss, hypovolemic shock, and an anaphylactoid reaction to intravenous pyelogram dye. Pulmonary edema developed and they subsequently passed large amounts of edema fluid through the endotracheal tube. Massive loss of plasma-like fluid from the lung required frequent evacuation of the endotracheal tube and intravenous replacement with large amounts of albumin-containing fluids. Both patients were treated with a volume respirator, positive end-expiratory pressure, 100% oxygen, corticosteroids, and tracheostomy. Both patients recovered from massive pulmonary edema with very severe hypoxemia and, 3 months afterwards, had normal pulmonary function, blood gas levels, and no evidence of pulmonary injury.

106. Administration of ketamine or Innovar by the microdrop technic: A double blind study. M. El-Naggar, J. Letcher, E. Middleton, and H. Levine. Anesth. Analg. 56: 279-282, 1977.

This study of 40 healthy adults undergoing elective gynecologic procedures was undertaken to evaluate the microdrip technic of administering ketamine or Innovar slowly to induce anesthesia and to supplement N_2O anesthesia. All patients were managed by the same anesthetist and surgeons and received 10 mg of diazepam and 0.4 mg of atropine IM for premedication. After injection of 10 mg of diazepam, anesthesia was induced by infusions containing either ketamine (2 mg/ml) or Innovar (0.1 ml/ml), at an average rate of 10 ml/min. The infusions were assigned to the patients randomly and their nature was disguised from the staff. After tracheal intubation, ventilation was mechanically supported and anesthesia maintained with N_2O-O_2 (2:1), by drip at a rate adjusted to the patient's vital signs, and by intermittent injections of 3 to 6 mg of d-tubocurarine. Special forms coded to suit computer use were used to collect data during induction, maintenance, and recovery, and standard mathematical tests were used for analysis.

Results showed that (a) ketamine effects could not be differentiated clinically from those of Innovar; (b) ketamine dosage could be reduced to 0.3 to 0.5 the recommended bolus dosage; (c) pulse rates and incidence of mental aberrations during induction or recovery were equal in both groups; (d) blood pressure showed a modest but significant increase (10% from basal values) until 20 min of tracheal intubation only in the ketamine group; (e) mean PaO_2 determined 30 min after tracheal intubation was significantly higher in the ketamine group; (f) ketamine administration by the slow (20 mg/min) microdrip technic reduces the incidence of side effects.

CLASSIFICATION OF REFERENCES

I. HUMAN STUDIES 5,6,8,13,16,20,25,27,28,29,30,36,41,55,62,83,84, 87,91,92,105

II. IN VITRO STUDIES 12,17,38,46,59,79,80,81,85,96

III. ANIMAL STUDIES:

A. Cats 21,43,69

B. Dogs 1,2,4,11,35,40,44,45,47,57,64,67,68,70,71,72,73,74,76, 77,78,79,80,81,82,88,100,102,103,104

C. Guinea pigs 14,97,98

D. Mice 18,50,53,60

E. Pigs 15

F. Primates, nonhuman

1. Baboon 10,33

G. Rabbits 9,32,34,49

H. Rats 19,22,31,37,39,51,52,54,56,58,61,75,89,93,94,95

I. Sheep 48

IV. REVIEWS 3,7,24,26,63,65,66,86,90,91,99,101

AUTHOR INDEX

UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER	UNCLASSIFIED
	2b. GROUP UNCLASSIFIED

3. REPORT TITLE

(6) ABSTRACT REFERENCE LIST: Reviews of Pertinent Literature in Shock,

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

(9) Technical Report,

5. AUTHOR(S) (First name, middle initial, last name)

(10) L. B. Hinshaw

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
(11) 27 Sept[illegible] 1977	56 (12) 59p.	106

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
(15) N00014-76-C-0229	(14) TR-120
b. PROJECT NO. NR 207-040	
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

Distribution of this report is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
	Office of Naval Research

13. ABSTRACT

Brief summaries of recent pertinent literature references in shock are included.

405916

DD FORM 1 NOV 68 1473 (PAGE 1)

UNCLASSIFIED